American Heart Journal

An international publication for the study of the circulation

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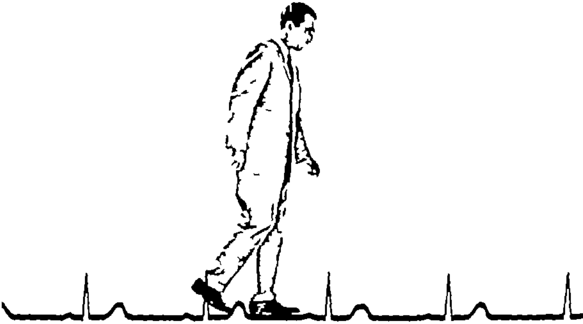
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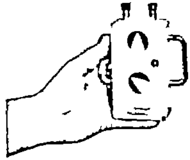
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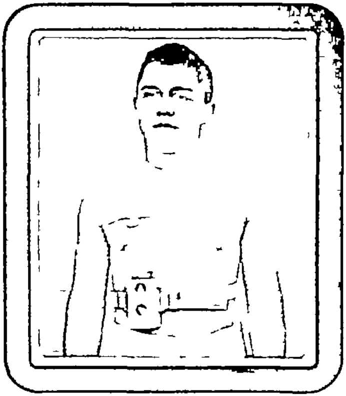
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U ed adjunct vely to other measures PRONESTYL (proca namide hyd ochloride) may frequently render a refractory arrhythmia controllable

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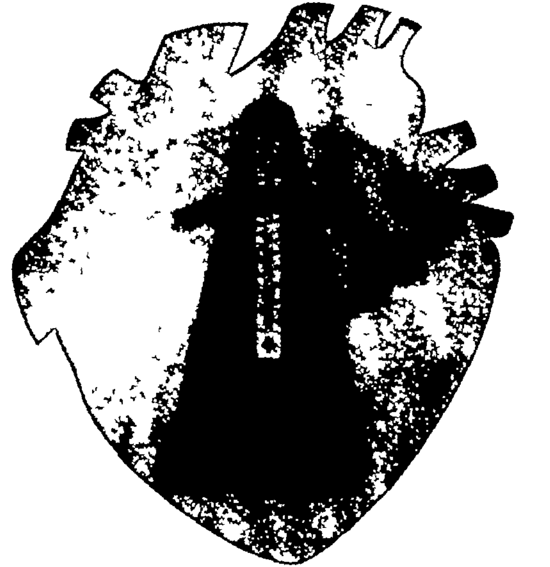
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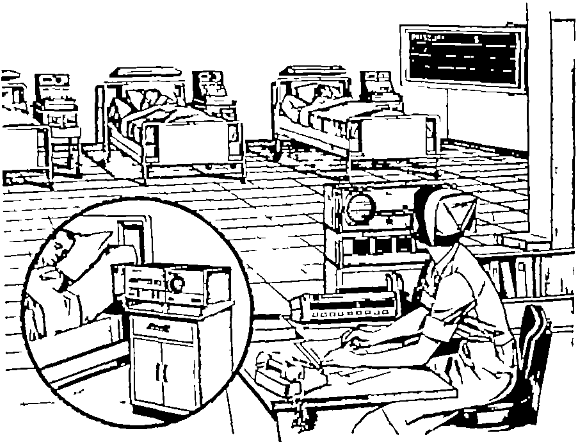
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American Heart Journal

January 1965 Volume 69 Number 1

Editorial

Cardioactive plasma substances

*T. E. Lowe, M.D., D.Sc.**
*Winifred G. Nayler, D.Sc.***
Melbourne, Australia

To physiologists, physicians, and surgeons the mechanism which controls the distribution of blood flow and pressure in the vascular system is of great interest, for the nature of this control is of importance to the understanding of abnormal states of the circulation as diverse as shock and hypertension.

Evidence is accumulating that this control has many of the characteristics of a servomechanism with feedback loops.[1] The receptors for these loops are situated in many parts of the circulation and are sensitive to pressure and chemical change. Transmission of signals from these receptors to the nervous integrating centers is by nerve pathways such as the carotid sinus and vagus nerves. On the effector side these loops act upon the musculature of the heart and blood vessels, but in contrast to the afferent side, communication from the integrating centers is partly over nerve pathways and partly over pathways that use the blood stream[2] as a carrying vehicle for cardioactive substances produced at various sites in the body.

A number of these cardioactive substances has been identified, and they include globulins, a group of polypeptides with differing actions, and the catecholamines. The physiologic significance of these substances has not yet been elucidated fully. However, their isolation from plasma does lend support to the concept that plasma substances play a role in regulating cardiovascular muscle activity.

The importance of the catecholamines for the integrity of the circulation needs no elaboration here, but the possible importance of the other cardioactive substances warrants some review of their properties. Especially is this so today, when for therapeutic reasons much of a patient's blood may be replaced with stored blood or an extracorporeal circulation may be placed in series with the body's circulation. Any of such procedures could conceivably interfere with the feedback loops of the control mechanism.

In addition to these circulating plasma substances, other cardioactive substances concentrated within the myocardium alone have been identified. Haberlandt's "automatic substance" or "heart hormone" is one of this group.

Within recent years, possibly as a direct result of the availability of exchange

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*Director, Baker Medical Research Institute; Commonwealth Reader Professor, Melbourne, Australia.
**Assistant Director, Baker Medical Research Institute, Melbourne, Victoria, Australia.

resins the plasma-distributed peptides angiotensin[4] and bradykinin[5] have been isolated and their chemical structure determined They are members of a series of dialyzable water and alcohol soluble polypeptides which appear when various enzymes act on the alpha 2 globulin fraction of plasma[6]

These polypeptides include the decapeptide angiotensin I and the octapeptide angiotensin II produced by the action of renin Angiotensin I and II together with several analogues of angiotensin II have been synthesized and their biologic activities investigated Angiotensin II has been shown to possess powerful vasoconstrictor and pressor properties its positive inotropic action has been demonstrated in a variety of experiments in which isolated cat papillary muscle preparations isolated guinea pig and rabbit hearts and dog heart lung preparations have been used[7] The positive inotropic activity of the octapeptide is however preceded by a marked but transient phase of negative inotropic activity which is accompanied by a decreased cardiac output and coronary flow This biphasic response to angiotensin II serves clearly to differentiate its mode of action from that of the catecholamines Red blood cells and plasma contain a peptidase which has a high degree of specificity for angiotensin II

The biologic significance of the angiotensins is unknown they represent a group of plasma transported cardioactive substances with properties suitable for components of the control mechanism of the cardiovascular system

When the alpha 2 globulin fraction of plasma is acted upon by the enzyme kallikrein a cardioactive nonapeptide kallidin[8] is formed The known properties of kallidin closely resemble those of another nonapeptide bradykinin[5] which is formed by the action of snake venom or trypsin on the plasma alpha 2 globulin fraction Kallidin and bradykinin both display marked biologic activity including the capacity to increase significantly cardiac output and stroke volume and at the same time to reduce peripheral vascular resistance and systemic arterial pressure Whether either of these peptides participates in the mechanisms normally responsible for the regulation of arterial pressures and peripheral vascular resistance remains to be determined but it does seem certain that the body is capable of producing such nonapeptides The duration of the effects of a single intravenous injection of bradykinin is very short and occupies 2 or 3 minutes only a finding which suggests that the body is equipped with an efficient mechanism for the regulation of plasma levels of bradykinin

Another cardioactive peptide (as yet unnamed) has been isolated directly from plasma[10] by means of acrylamide gel filtration[11] This particular polypeptide the molecular weight of which lies within the range 7 000 to 8 000 has been isolated from heparinized plasmas of a wide variety of species including man Its positive inotropic activity has been demonstrated on isolated rat and toad hearts and on dog papillary muscle preparations The intravenous injection of this plasma polypeptide into rabbits anesthetized with Nembutal results in raised arterial blood pressures increased cardiac output and increased right and left ventricular pressures Its mode of action therefore is essentially different from that of either angiotensin or bradykinin

Other substances present in plasma and known to be cardioactive include the protein complex isolated by Hajdu and Leonard This particular complex consists of three globulins designated as cardioglobulin A B and C The positive inotropic activity of the complex depends upon the simultaneous presence of all three Cardioglobulins have been isolated from the plasma of most species of mammals and their activity has been shown to vary in the presence of certain cardiac disorders including aortic stenosis and hypertension[12]

At a time when many biologists are endeavoring to elucidate the precise mode of action of certain ions in the maintenance and regulation of cardiac muscle it should not be forgotten that plasma-distributed substances including peptides such as those mentioned above may regulate the permeability of cell membrane including those of cardiac muscle

Speculation concerning the role of these substances in human disease would be pre

mature but previous experience with catecholamines and angiotensin suggests that they will continue to evoke the interest of clinicians

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Clinical communications

Ventricular septal defect in infancy

A hemodynamic study

Langford Kidd, M.D., M.R.C.P.Ed.
Vera Rose, B.Sc., M.B., B.S.
George Collins, M.B., Ch.B.
John Keith, M.D.
Toronto, Canada

At the present time it is not clear what course an infant presenting with a ventricular septal defect is likely to follow. Although the great majority of children will never be a cause for concern,[1] we know that some will develop the Eisenmenger reaction[2] (shunt reversal due to increased pulmonary vascular resistance), some will have continuing disability due to increased pulmonary blood flow,[3] and in yet others the defect will decrease in relative size or even close spontaneously.[4] Since ventricular septal defect is the most common form of congenital heart disease and since it is not clear from the data in the literature on infants[5] what the hemodynamic picture is or what changes are occurring at this age, hemodynamic data obtained from 151 infants who were catheterized in this department before their first birthday and in whom ventricular septal defect was the sole diagnosis were reviewed. Twenty-five of these patients were restudied subsequently at intervals from 1 to 9 years and these data are also presented.

Methods

Routine catheterization procedures were used. All but the very young were lightly sedated with chlorpromazine, meperidine, and promethazine (C.M.P.).[10] Pressures were recorded using Statham P23Db strain gauges at a reference level one third of chest thickness below the sternum and recorded on a Sanborn four-channel direct-writer recorder and later on an Electronics for Medicine DR8 recorder. Oxygen saturations and contents were assessed using a Wood oximeter and Van Slyke analyses. Oxygen consumption was calculated in all instances using a figure of 180 ml. per square meter per minute.[11] The pulmonary artery was entered in all patients and a valid wedge pressure was secured in 65 per cent. *Total* pulmonary vascular resistance was calculated throughout; calculations using pulmonary perfusion pressures in those patients in whom it was available showed *some alteration* in absolute values but little change in intragroup relationships. In 35 per cent of the patients either the systemic arterial pressure or the systemic oxygen saturation was not recorded or neither. Cuff pressure (mean $\frac{S + 2D}{3}$) was used when necessary; oxygen saturation was assumed to be

From the Department of C[illegible] and the Research [illegible], The Hospital for Sick Children, Toronto, and the Department of [illegible], University of Toronto, Toronto, Canada.
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[illegible] The Research [illegible], The Hospital for Sick Children, 555 University Ave., Toronto 2, Ont., Canada.

95 per cent unless pulmonary hypertension was present or sedation was noted to be heavy and systemic desaturation was considered to be a possibility All patients in whom the hemodynamic data were inadequate or suggested a possible associated lesion were excluded from the study Data were entered on IBM punch cards and calculations and analyses were made by the IBM 7090 computer at the Institute of Computer Science University of Toronto using conventional Fick formulae

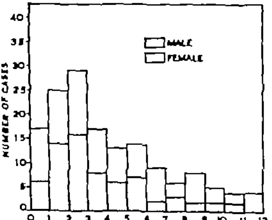


Fig 1 Age distribution of patients at time of cardiac catheterization

Results

Catheterization under 1 year of age

AGE AND SEX Age at the time of study and the sex distribution of the 151 infants is illustrated in Fig 1 It can be seen that 58 per cent of the infants were studied in the first 4 months of life and that 55 per cent were females and 45 per cent were males

PULMONARY BLOOD FLOW The pulmonary blood flow is illustrated in Fig 2 plotted against the systemic blood flow in each case Although the systemic blood flow varied narrowly between 400 and 2 000 ml per minute the pulmonary blood flow varied widely between 500 and 7 000 ml per minute The majority of patients had pulmonary to systemic flow ratios between 2 1 and 5 1 but 22 per cent had low flow ratios (less than 2 1)

PULMONARY ARTERIAL PRESSURE Fig 3 demonstrates the relationship of mean pulmonary arterial pressure to mean systemic arterial pressure in each case Although the systemic mean pressure varied between 50 and 80 mm Hg the pulmonary

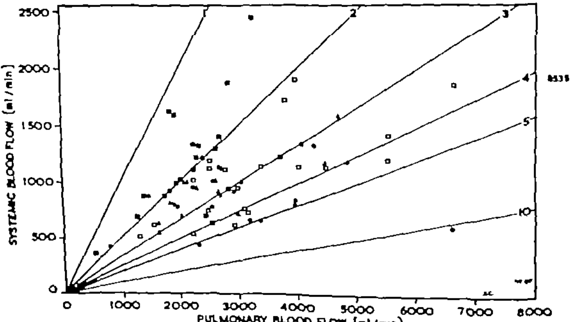


Fig 2 Distribution of pulmonary and systemic blood flow in each case The oblique lines represent pulm to systemic flow ratios Those patients with flow ratios less than 2 1 are indicated by solid symbol

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[illegible] The Hosp[illegible] 555 Univer[illegible] Ave., Toronto 2, Ont., Canada.

ranged from 10 to 70 mm Hg It will be noted that the patients with flow ratios less than 2 1 can be divided into two groups those with pulmonary arterial pressures between 13 and 43 per cent of systemic (16 per cent of the total) in whom the size of the pulmonary blood flow was obviously determined by the small size of the defect and those with pulmonary arterial pressures between 50 and 93 per cent of systemic (6 per cent) in whom although the size of the defect played some part the pulmonary vascular resistance was the chief determinant of pulmonary flow

PULMONARY VASCULAR RESISTANCE Total pulmonary vascular resistance varied between 300 and 2 000 dynes sec cm $^{-5}$ and total systemic vascular resistance between 2 000 and 10 000 dynes sec cm $^{-5}$ (Fig 4) The systemic to pulmonary resistance ratios were mostly greater than 5 1 the patients with *flow ratios* greater than 2 1 have been divided arbitrarily into three groups for the purposes of follow up those with moderate pulmonary vascular resistance (resistance ratios between 5 1 and 7 1) those with low pulmonary vascular resistance (ratios greater than 7 1) and those with higher resistance (ratios less than 5 1)

VARIATION WITH AGE No correlation between any of these parameters and age could be discovered There was no variation in the scatter of the findings when they were plotted by month

Subsequent recatheterization

CHANGE IN FLOW Twenty five patients were recatheterized at intervals varying from 1 to 9 years In 19 patients the flow ratio had decreased (Fig 5) In 6 no significant left to right shunt could be demonstrated and one of these had a significant right to left shunt

CHANGE IN PRESSURE When the relationship of mean pulmonary arterial pressure to mean systemic arterial pressure on each occasion was studied (Fig 6) it was seen that in the majority the pulmonary arterial pressure was lower relatively than at the time of the first study No patient developed a significant gradient across the right ventricular outflow tract Three of the patients who had no significant shunt at the time of the second study were in this group in view of the disappearing shunt and the fall in pulmonary arterial pressure in these 3 the septal defect was considered to have closed functionally at least

Fig 7 illustrates changes in flow and pressure ratio simultaneously Twenty four per cent of the patients may be said not to have changed significantly and 16 per cent to have had increased pulmonary blood flow Of the 60 per cent who had decreased flow the mean pulmonary arterial pressure had increased in 32 per cent demonstrating a trend to the Eisenmenger reaction In 28 per cent the flow and pressure had both decreased which suggests that the relative size of the defect was less

CHANGE IN RESISTANCE When change in the systemic to pulmonary resistance ratio was plotted against time (Fig 8) it could be seen that in 14 cases (56 per cent) the ratio had decreased (pulmonary vascular resistance increased) and in the remainder (44 per cent) it had increased (pulmonary vascular resistance decreased) It is of interest to note that all in the group with increasing resistance had flow ratios greater than 2 1 and 8 had resistance ratios greater than 7 1 at the time of the first study in

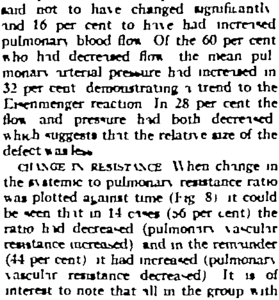


Fig 5 Change in pulmonary to systemic flow ratios with time between first and second catheterizations Symbols as in Fig 4 E Patients with bidirectional shunting C Patient in whom there has been functional closure of the defect

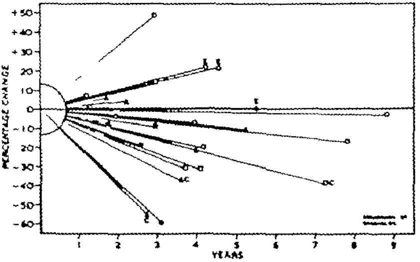


Fig. 6. Change in mean pulmonary arterial pressure × 100/mean systemic arterial pressure between first and second catheterizations. Symbols as in Fig. 5.

infants, whereas in the group with decreasing pulmonary vascular resistance 2 had low flow and high resistance at that stage.

Discussion

Ventricular septal defect is the most common of the congenital heart defects. The course of the disease in cases in which this is the sole diagnosis has recently been the object of increased attention.[1-11] Among the questions at issue are these: (1) Are children with low pulmonary blood flow and high pulmonary vascular resistance in this state from birth[3] or do they develop this state subsequent to a period of high flow and low resistance in the pulmonary vasculature?[24] (2) What are the hemodynamic groupings for infants with this defect?

The present study demonstrates the spectrum in 151 infants presenting with a ventricular septal defect who were catheterized before their first birthday. It will be clear that this group is not representative of all children with this lesion nor is it a random sample of all infants under 1 year of age. It is rather a selected group of infants who were catheterized early, either because they were in difficulty or because the diagnosis was not absolute. At one extreme of the spectrum is a small group (16 per cent of the total) who have small pulmonary blood flow and low pulmonary vascular resistance, in whom the size of the defect will ensure that no sequelae due to the shunt will occur in later life. This small group is probably representative of a much larger group exactly similar who were not catheterized because their characteristics were obvious without study. At the other extreme is a group with a small shunt and high pulmonary vascular resistance (6 per cent of the total). In between lies the large majority (78 per cent) of the patients, those with flow ratios of over 2:1. These cases were arbitrarily divided on the basis of resistance ratio into three groups corresponding to low, normal, and high pulmonary vascular resistances.

It is not clear whether the group with small shunt and high resistance represent the so-called "congenital Eisenmenger" group described by Wood or are simply patients who are slow to lose their fetal blood vessel architecture, for it must be borne in mind that the pulmonary vascular resistances of these patients must be compared with the varying resistances in normal children (ranging from a systemic to pulmonary resistance ratio of 1:1[8] at moments after birth to 5:1 in the first year and not reaching the adult ratio of 10:1 until later[14]). However, 2 of these patients with low flow and high resistance were found at recatheterization to have a considerably lower resistance, which suggests

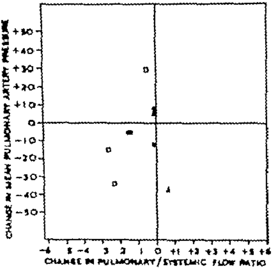


Fig 7 Change in pulmonary to systemic flow ratio plotted against change in mean pulmonary arterial pressure in each case Symbols as in Fig 5

that they were slowly losing the medial hypertrophy of the fetal vascular pattern

When we examine the group with a flow ratio over 2 1 40 per cent had low resistance (systemic to pulmonary resistance ratio over 7 1) and of these 10 were recatheterized Two had a still further reduced pulmonary vascular resistance and the other 8 showed increased resistance some to an extreme degree in 2 of these the progressive pulmonary vascular obstruction had advanced to the point of flow reversal Nineteen per cent had resistance in the normal range (ratios between 5 1 and 7 1) and of these 4 have been recatheterized One had a still further reduced pulmonary vascular resistance in one the defect had closed and 2 had developed increased resistance Nineteen per cent had high resistance (ratios below 5 1) and of these 8 were restudied 4 had a reduced resistance in 2 of whom the defect had closed and 4 had a further increased resistance

It would appear likely then that since the pulmonary vascular resistance drops rapidly in the weeks after birth the shunt through a large ventricular septal defect will tend to be large its size will be limited by the ratio of systemic to pulmonary vascular resistance and the capacity of the left ventricle to supply the shunt This situation was found in 78 per cent of our patients in 19 per cent the pulmonary vascular resistance might be considered to have been increased although the shunt was still large In only 6 per cent of the total was high pulmonary vascular resistance found to be responsible for a lowered pulmonary blood flow it seems probably that these patients are slowly losing their fetal vascular patterns rather than acquiring progressive pulmonary vascular obstruction The limited recatheterization data suggest that the patients who have high pulmonary blood flow and low to moderate pulmonary vascular resistance during infancy are the ones who are in danger of developing vascular obstruction and that they may do this early in life This is in broad agreement with studies from other centers[1 8 9] Evidence is also accumulating that increased pulmonary vascular resistance may increase still further after surgical closure of the defect[11 4] It is obviously important then to recognize these cases before the vascular changes are too far advanced and it should be possible to do this by recatheterizing at 2 and possibly again at 4 years of age the patients

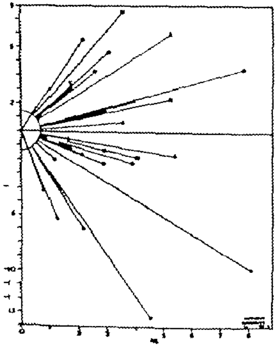


Fig 8 Change in ratio of systemic to pulmonary resistance between first and second catheterizations Symbols as in Fig 5

who were studied in infancy and found to be at risk. If there is evidence of increasing resistance at the time of either of these studies the patient should be submitted to operation forthwith. This course of action has much to recommend it.

However the selected nature of the group and the small numbers who underwent serial study makes definite conclusions difficult. This study of the natural history of ventricular septal defect with clinical electrocardiographic and hemodynamic correlation is continuing and will be reported subsequently.

Summary

The hemodynamic data are reported in 151 infants in whom the sole diagnosis was ventricular septal defect and who underwent cardiac catheterization before the age of 1 year.

Seventy eight per cent had pulmonary to systemic flow ratios over 2 1 and in 16 per cent the low pulmonary blood flow (flow ratio under 2 1) was due to a small defect. Fifty nine per cent of the patients had low or normal total pulmonary vascular resistance and in only 25 per cent was resistance increased above normal for his age group.

Twenty five of the patients were recatheterized subsequently and it was found that in three the defects had achieved functional closure. Two patients who were in the group with low flow and high resistance at the time of the first study had lower resistance later. Of the 14 patients who demonstrated increasing pulmonary vascular resistance 10 had low or normal resistance earlier.

It is suggested that progressive pulmonary vascular obstruction is a sequel to high flow and low vascular resistance in the pulmonary circulation and is not present from the time of birth. It is proposed that such patients be subjected to serial study in order to define those who are reacting to the pressure flow stimulus in this way.

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Myocardial ischemia after maximal exercise in healthy men

A method for detecting potential coronary heart disease†

*Allen E. Doan, M.D.**
Donald R. Peterson, M.D.
John R. Blackmon, M.D.
Robert A. Bruce, M.D.
Seattle, Wash.

Myocardial infarction in previously asymptomatic men often is the first manifestation of coronary heart disease. Regardless of therapy, initial infarction is associated with a substantial mortality rate within the first month. These two facts illustrate the urgent need for accurate methods of detection of potential coronary heart disease. If this could be identified accurately in healthy men, the relative importance of diet, smoking, drugs, and physical activity on the natural history of this disease might be ascertained more effectively.

Electrocardiography is the most sensitive method available to epidemiologists for the detection of myocardial ischemia presumably due to this disease. Furthermore, for the detection of coronary heart disease, electrocardiographic responses to exercise exceed the value of resting 12 lead electrocardiograms.[3] Despite prolonged uncertainty over criteria, the double Master two step test[4,5] has improved the detection of individuals who develop clinical coronary disease within a few years. Mattingly[6] showed by autopsy study of men dying years after the test that abnormal segmental S-T depression signifies diffuse and advanced coronary artery disease. Therefore, myocardial ischemia due to less advanced disease might be detected in apparently healthy individuals by a more strenuous test involving maximal exercise. To test the validity, safety, and feasibility of this hypothesis, a prospective study of maximal exercise testing was initiated in several hundred men.

This paper reports the initial results of a study conducted conjointly by the Seattle-King County Department of Public Health, the Division of Cardiology, Department of Medicine, University of Washington, and the Seattle YMCA.

Definitions

The term *potential coronary heart disease* designates those who have no clinical evidence of coronary disease except for electrocardiographic demonstration of myocardial ischemia after exercise testing. It implies no current proof that in a prospec-

From the Seattle-King County Department of Public Health and the Division of Cardiology, Department of Medicine, University of Washington, Seattle, Wash.

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*Address: Seattle-King County Department of Public Health [illegible]

tive study the etiology is coronary atherosclerosis but it does imply a high potential risk for *future* overt coronary heart disease. Not all men with potential coronary heart disease will necessarily develop overt disease and conversely some eventually might exhibit overt disease without preceding evidence of potential disease. The term *latent coronary heart disease* is avoided since it implies objective evidence that any myocardial ischemia is indeed due to this specific etiology, even though a retrospective study may subsequently establish its presence.

Materials and methods

1. Population. A total of 433 male volunteers 10 to 82 years old was examined. Included in the group were 170 boys and men 10 to 30 years old who were members of physical education classes in elementary or high schools or the University of Washington,[7] 38 men 30 to 60 years old (90 per cent under 40) who were employees of the Boeing Company, and 225 men 35 to 82 years old who were members of the Seattle YMCA.

The YMCA men were preselected according to their exercise habits by age and attendance criteria from the membership files. The active group included men who regularly exercised at the YMCA at least twice weekly for 1 year preceding the examination. The inactive group was composed of men who exercised at the YMCA five or less times in the entire preceding year. Of 337 eligible men, 225 accepted an invitation to participate and they were examined. They also completed an activity diary which tabulated any physical activity outside the YMCA. On the basis of the attendance criteria and diary information the 225 men were arbitrarily divided, 114 to the active group and 111 to the inactive group. The possible effects of regular physical activity on coronary heart disease in these two groups will be assessed after future examinations.

No one in the study had a history of previous myocardial infarction and no one was taking digitalis.

2. Examination procedures. The 225 YMCA members underwent a comprehensive examination including cardiovascular history and physical examination, resting 12 lead electrocardiogram, chest x-ray, determination of hematocrit and serum cholesterol, double Master's two-step test, and the multistage exercise capacity test as defined elsewhere.[10,11]

The 208 men from the physical education classes and the Boeing Company underwent a less comprehensive examination including a cardiovascular history and physical examination, resting 12 lead electrocardiogram, and the multistage exercise capacity test. These men did not have chest x-rays, blood studies, or double Master's two-step tests.

3. Exercise testing. The standard double Master's two-step test was performed using Master's revised tables and his standard 9 inch steps.[4,5] The test was monitored clinically and electrocardiographically according to Lepeschkin's detailed instructions.[6]

The multistage exercise capacity test measures capacity for exercise on a treadmill of any ambulatory individual by means of progressive increases in speed and grade without interruption through seven consecutive 3 minute stages (see Table I). The test starts with a slow walk on a slight incline and concludes with a fast run up a steep grade. The subject is permitted to grasp a handrail on the treadmill to prevent stepping off to the side of the conveyor belt during running; he is not permitted to lean or to pull on this support. Since very few men are capable of completing the entire 21 minute test, each man is instructed to run until he considers himself exhausted, then signal for the treadmill to be stopped. The attending physician stops the treadmill only if the subject develops a faltering gait or other clinical symptoms such as exertional hypotension. The only

Table I. Multistage exercise capacity test

Stage	Speed (m.p.h.)	Grade (%)
First	1.7	10
Second	5	12
Third	3.4	14
Fourth	4	16
Fifth	5.0	18
Sixth	5.5	20
Seventh	6.0	2

Table II. Cardiovascular abnormalities detected without exercise testing

Diagnosis	*Number of men*	*Abnormal exercise test*	
		Master	*Maximal*
Hypertension* with left ventricular hypertrophy	5	3	4
Hypertension without evidence of heart disease	5	0	1
Aortic stenosis	4	2	3
Angina pectoris	3	3	3
Silent myocardial infarction	2	0	1
Atrial septal defect	1		
Widened QRS-T angle resting ECG†	1	0	1
Cardiomegaly atrial fibrillation hypertension (?)	1		
Borderline hypertension with left ventricular hypertrophy	1		
Right bundle branch block with sinus arrest and nodal escape	1		
Total	24	8	13

*Hypertension = both systolic ≥ 160 mm Hg and diastolic ≥ 95 mm Hg. Left ventricular hypertrophy by [illegible] ECG or chest x-ray film.
†D[illegible] [illegible] of r[illegible] 12 lead electrocard[illegible]

electrocardiographic indication for stopping the test is the appearance of ventricular tachycardia. The appearance of premature beats or ischemic segmental S-T depression is not sufficient reason for stopping the test. Electrocardiographic monitoring is done before the test while the subject is seated on a chair on the treadmill, during each minute of the test while the subject is walking and running, and for a minimum of 3 minutes after the test while the subject is again seated. If the electrocardiogram is abnormal 3 minutes after the test, monitoring is continued until the tracing returns to normal. A single bipolar precordial lead is used with small adhesive snap-on electrodes placed at the V_5 position and beneath the tip of the right scapula. The resulting electrocardiogram has the appearance of a standard V_5 precordial lead in most instances.

All 433 men (and boys) completed the entire battery of tests without incident. Ventricular tachycardia was not seen during any of the maximal exercise capacity tests; thus none was stopped for electrocardiographic reasons. The usual clinical reasons for stopping the treadmill were dyspnea, generalized or specific fatigue, and tiredness of the calf muscles. Discovery of a cardiovascular abnormality did not alter the individual's testing program. For example, all men with positive double Master's two-step tests still performed the multistage exercise capacity test.

Rec[illegible] th[illegible] [illegible] lead has been added t[illegible] p[illegible] d[illegible] better [illegible] of th[illegible] d[illegible] part of th[illegible] heart [illegible] th[illegible] lead [illegible] th[illegible] right scapula [illegible] electrod[illegible] [illegible] placed [illegible] t[illegible] th[illegible] [illegible] corresponds to modified Lead II

Criteria

Normal. All the men included as cardiovascular normals in the following discussion have met the following requirements: (1) No history of cardiovascular disease. (2) No evidence of cardiovascular abnormalities on physical examination. Seated men with resting blood pressure in the right arm of 160 mm Hg or higher systolic and 95 mm Hg or higher diastolic were considered to be hypertensive. Persons with either systolic or diastolic pressures below these levels were considered to have normal blood pressure for purposes of this study. (3) Normal heart configuration on chest x-ray film. (4) Normal resting 12 lead electrocardiogram.

Electrocardiographic. Robb, Marks, and Mattingly[11-14] convincingly demonstrated by long-term actuarial follow-up study of nearly 1,000 men that ischemic segmental S-T depression was the only unequivocal postexercise electrocardiographic change associated with the later appearance of overt coronary heart disease. For that reason, the only criterion for a positive double Master's two-step test was 0.5 r

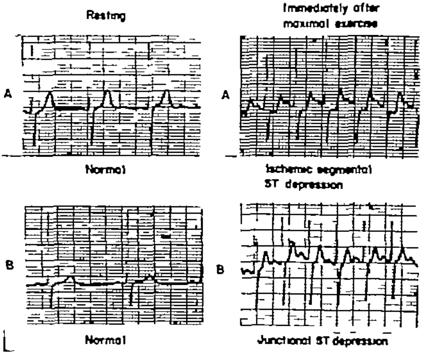


Fig 1 A and B represent normal precordial lead electrocardiogram taken at rest before the maximal exercise capacity test of 2 men who were considered to be normal after their clinical evaluations. *Both* men had normal double Master test. Duration of the maximal exercise capacity test and maximal heart rate were similar in both men. A illustrates the abnormal ischemic segmental S-T depression Subject A after maximal exercise which establishes the diagnosis of potential coronary heart disease (see text). *B* illustrates the junctional S-T depression in Subject *B* after maximal exercise which is considered not to be abnormal.

or more of ischemic segmental S T depression. The only criterion for a positive ischemic response in the maximal exercise capacity test was 1 0 mm or more of segmental S T depression (Fig 1).[13] The appearance of this ischemic response in otherwise normal individuals constitutes the only basis for a diagnosis of potential coronary heart disease. Junctional S T changes, transient conduction defects, and premature atrial or ventricular beats were considered to be within the range of normal on all the exercise electrocardiograms.

Results

1 Detection of cardiovascular abnormalities in host exercise testing. No overt cardiovascular abnormalities were found by the less comprehensive examination in 170 younger men and boys in the physical education classes or in 38 Boeing Company personnel.

Twenty four of the 225 YMCA men (10 6 per cent) had cardiovascular abnormalities detected by the initial history, physical examination, chest x-ray film and or resting electrocardiogram. A tabulation of the abnormalities found in these 24 men is shown in Table II. The other 201 YMCA men had normal cardiovascular history and physical examinations and no significant chest x-ray or resting electrocardiographic findings.

2 Detection of myocardial ischemia with maximal exercise testing. Of the 433 men who performed the multistage exercise capacity test, 32 exhibited ischemic segmental S T depression. Thus the over all prevalence of myocardial ischemia was 7 4 per cent. The prevalence varied directly with age, rising from 0 per cent in the 170 men under 35 years of age to 28 per cent in 32 men 50 to 54 years of age (Fig 2). In the age interval 55 to 59 years the preva-

lence decreased to 19 per cent and then resumed its rise to 46 per cent in those men who were over 60 years of age The greatest rise in abnormal tests occurred in the 45 to 49 age group and the 60+ age group The decline in prevalence in the late fifties is not adequately explained but the small sample size is a probable reason It is also possible that some of the decline may have resulted from the loss of positive responders due to death from coronary heart disease

Since hematocrits ranged from 39 to 54 per cent with a mean of 47 per cent myocardial ischemia was not the result of anemia

3 Comparison of double Master s test and maximal exercise test

CLINICALLY NORMAL MEN Of the 201 YMCA men with no cardiovascular abnormalities who performed the double Master s two-step test only 2 exhibited a positive electrocardiographic response of ischemic segmental S T depression When these same 201 men performed the multistage exercise capacity test 18 showed a positive electrocardiographic response Thus on direct comparison the maximal exercise test was nine times more likely to elicit this response than the conventional double Master s two step test

CLINICALLY ABNORMAL MEN Of the 24 YMCA men with clinically detectable cardiovascular abnormalities 8 (33 per cent) had positive double Master s tests

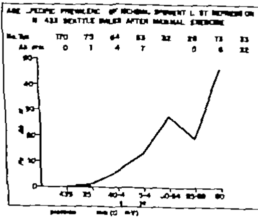


Fig 2 Increasing total prevalence of potential and overt coronary heart disease in relation to advancing age on the basis of ischemic segmental S-T depression recorded immediately after maximal exercise in healthy boys and men

Three of the 8 men had angina pectoris 3 had hypertension with left ventricular hypertrophy and 2 had aortic stenosis All of these 8 men also had positive responses to maximal exercise (Table II) In addition the multistage exercise capacity test was positive in 5 men with abnormalities who had negative double Master s tests Thus in the men with clinically detectable cardiovascular abnormalities the maximal exercise test was 62 per cent more sensitive than the double Master s test

Again with reference to Table II it is apparent that one man with a healed silent diaphragmatic infarction had both a normal double Master s test and a normal treadmill test Although this is quite possible if the infarction occurred in the only area of ischemic myocardium an alternative explanation is inadequate monitoring of the diaphragmatic surface with a single lead electrocardiogram

Discussion

Previous studies utilizing the electrocardiogram after exercise tests in normal males are summarized in Table III The list is long and the numbers tested are many but very few helpful conclusions can be drawn from the studies since the methods of exercise the ages of the men examined and the electrocardiographic criteria are so varied The range of positive tests from 0 per cent to 37 0 per cent in normal males serves to emphasize the variability Since the late nineteen fifties when ischemic segmental S T changes began to be used as the major criterion for positive tests the results have been more nearly comparable The men in normal populations who have exhibited this evidence of myocardial ischemia after exercise are not false positives as was initially thought Follow up examinations have shown that these men have a much higher risk of future clinical coronary heart disease than does the general population Although the yield is small the exercise tests used to date have identified a few men with latent but advanced coronary heart disease

The importance of exercise testing for the detection of potential coronary heart disease is illustrated in Table IV In the Los Angeles [9] and Framingham[34] studies in which the methods of diagnosis

Table III Prevalence of abnormal postexercise electrocardiograms in normal males

Author Year	Exercise method	Number examined	Age range (yr)	Abnormal (all criteria)	Per cent abnormal	Ischemic ST depression	Per cent ST depression
Master 1942	SM and DM	58	40–68	0	0 0	0	0 0
Mayer[14] 1944	DM	88	21–56	7	8 0	?	?
Unterman 1948	SM and DM	37	?	4	10 8	?	?
Scherlis 1950	SM and DM	95	17–57	4	4 2		
Thomas[19] 1951	DM	244	20–35	6	2 5	?	?
Leeds[8] 1953	SM	526	<40(283) >40(263)	11	2 1	11	2 1
Wener[20] 1953	SM and DM	150	15–60	9	6 0	?	?
Russek[21] 19 6	DM	108	40	0	0 0	0	0 0
Manning[22] 1957	DM	200	18– 4	1	0 5	1	0 5
Bengtsson 195	Bicycle ergometer to heart rate of 150	19	15–40	0	0 0	0	0 0
		77	15–60	2	2 6	2	2 6
Mason[23] 1959	SM and DM	94	20–69	13	13 8	?	?
Brody[24] 1959	DM	756	36–63	280	37 0	23	3 0
Rumball[27] 1963	66 steps†	660	19–54	90	13 6	31	4 7
Master 1961	DM	237	15–79	6	2 5	4	1 7
Mattingly 1962	DM	300	25–60	6	2 0	6	2 0
Bellet[8] 1962	Bicycle ergometer 20-25 m p h × 3 min	135	17–64	14‡	10 0	14	10 0

SM and DM [illegible] d double Master [illegible] respectively
†[illegible] down [illegible] up 66 steps.
‡[illegible] d [illegible] cases [illegible] due [illegible]

cally overt coronary heart disease included the history physical examination and resting electrocardiogram the case detection rate was 14 and 24 per 1 000 respectively. The larger Chicago[11] study used similar diagnostic methods and detected 26 cases per 1 000 men. The use of mild exercise first in the form of the double Master's test and later as a low speed treadmill test in the Albany[12] study increased the prevalence of both overt and potential coronary heart disease to 38 cases per 1 000. Brody[6] also observed a similar rate of 30 cases per 1 000 in 756 clinically unselected business executives who performed the double Master's test.

In contrast to these studies clinical examination and the multistage exercise capacity test yielded a much higher total prevalence rate of 136 per 1 000 in the Seattle study (Table IV). Despite the small number of men examined in this age group the difference in detection rates for *potential* coronary heart disease is highly significant. At the 95 per cent confidence level the minimal rate for the current Seattle study is 47 cases per 1 000 which is 1 3 times the maximal detection rate for overt coronary heart disease of 36 cases per 1 000 for those studies using no exercise testing methods. Compared in the same manner to the Albany study *in which mild exercise* tests were used the minimal detection rate for potential disease in the Seattle study was 3 3 times higher. At the 95 per cent confidence level the total prevalence of potential and overt coronary heart disease identified by the Seattle study is at least 190 per cent of that reported in the Albany study.

Table V compares the prevalence of potential coronary heart disease in London[7,11,31] and Seattle men of 40 to 54 years of age who were considered to be normal on the basis of clinical examinations x-ray films of the chest and resting electrocardiograms. A surprisingly high prevalence of myocardial ischemia in normal men (i.e. potential coronary heart disease) was revealed by both studies 67 per 1 000 in London and 95 per 1 000 in Seattle. In fact the prevalence rates in

these normal men surpassed the rates for detection of overt coronary heart disease of the populations in the studies referred to above. Without strenuous exercise testing men in the London and Seattle studies with potential coronary heart disease would not have been detected. Whether the multistage exercise capacity method is superior to the milder English exercise method of running down and up 66 stairs must await further observation of the maximal exercise test. The wide range of values at the 95 per cent confidence level makes it difficult to predict at this time which test is more sensitive.

It is important to emphasize, however, that electrocardiographic evidence of myocardial ischemia does not define its etiology. Under these conditions, where clinically overt disease was not detected, anemia was excluded, and other data indicate a common occurrence of coronary atherosis in this population, it is indeed likely that in future follow-ups clinically apparent coronary heart disease may be revealed in many who showed this response. Undoubtedly other explanations will be found in some, just as some negative responders will indeed exhibit coronary heart disease eventually. Nevertheless Master,[8] Brody,[9] Mattingly,[9] Robb,[11] and Rumball and Acheson[27] have all established that electrocardiographic evidence of myocardial ischemia after exercise tests identifies individuals with a high risk of future coronary disease. Since the detection rate depends on the degree of exercise used, a maximal exercise capacity test should be the most sensitive method for identifying a high risk population. The high detection rate of myocardial ischemia in this study supports that hypothesis. Presumably

Table IV. Total prevalence of potential and overt coronary heart disease in men 40 to 54 years old in several populations

Location	Methods of diagnosis	Examined	Cases	Rate per 1,000	Confidence intervals: 50 per cent level	Confidence intervals: 95 per cent level
Los Angeles	History, physical examination, resting ECG	697	10	14	11–19	7–27
Framingham	History, physical examination, resting ECG	990	24	24	22–28	16–36
Chicago	History, physical examination, resting ECG	3,229	84	26	24–28	20–32
Albany	Same as above plus moderate treadmill exercise test	1,821	69	38	35–41	29–47
			15	8	7–11	5–14
Seattle	Same as above plus maximal treadmill exercise test and double Master's test	132	18	136	110–160	89–215
			12	91	73–115	47–159

*Men with potential coronary heart disease excluded [illegible]

Table V. Potential coronary heart disease in clinically normal men of 40 to 54 years of age

Location	Methods of diagnosis	Examined	Cases	Rate per 1,000	Confidence intervals: 50 per cent level	Confidence intervals: 95 per cent level
London	ECG after run down and up 66 steps	284	19	67	56–80	40–104
Seattle	ECG during and after maximal treadmill exercise test	176	12	95	80–170	49–167

these men have less advanced potential coronary artery disease than do those asymptomatic men with positive double Master's tests since more cardiovascular stress was required before myocardial ischemia developed If the disease is detected at an earlier stage the time interval between detection and onset of clinical disease will be prolonged This will allow more time for the objective study of certain factors which might influence the course of coronary heart disease

We concur with Simonson[3] that ischemic segmental S-T depression cannot be produced in normal young persons by the most severe exercise None of the 170 men under 35 years of age developed ischemic segmental S T depression although their maximal heart rates during exercise were over 200 in many cases Minimal junctional S-T depression of less than 1 5 mm was so common as to be practically universal in this age group The finding of myocardial ischemia after exercise follows the same age distribution as that for coronary heart disease (Fig 2) In this country where coronary heart disease is so common in middle-aged men it is tempting to conclude that this finding indeed represents latent coronary heart disease when other causes (anemia aortic stenosis etc) have been excluded however this presumption must await future examinations of these men

To date 125 of the 225 YMCA men (55 per cent) have been re-examined 1 year after the initial evaluation Included in this group are 15 men who had abnormal maximal exercise electrocardiograms at the time of the first examination Thirteen of the 15 men (87 per cent) had similar abnormal electrocardiograms at the time of the second examination Five other men have abnormal electrocardiograms this year who had normal electrocardiograms on the first examination The clinical histories of the men examined to date have not changed No one has suffered a myocardial infarction and no deaths have occurred in the study population Follow up to date has been unexpectedly high at 97 per cent

The reproducibility of the test results is encouraging Since the tracings during exercise have improved considerably in technical quality the future results of examination should be even more reproducible The problem of obtaining consistently readable electrocardiograms during the sixth and seventh stages of the test remains but the tracings obtained immediately after exertion are quite satisfactory

The sensitivity of this method has been referred to earlier In the initial examination only 6 of the 18 cases (33 per cent) of myocardial ischemia were found by the usual examining methods including the double Master's test The other 12 cases (67 per cent) were detected solely by the maximal exercise test electrocardiogram The maximal exercise test therefore tripled the detection rate for total prevalence of coronary heart disease in this small group of men

The safety of this testing procedure has been established during the past 3 years The true risk is unknown since no difficulty has been encountered in 2 000 maximal exercise examinations Over 1 200 of these tests were done on cardiac patients including 800 patients with angina or proven myocardial infarction who were being evaluated for rehabilitation purposes[18] No instance of myocardial infarction has been induced by this test The test is always monitored by an experienced physician and is never done in the presence of an acute illness or acute changes on the resting 12 lead electrocardiogram A brief cardiovascular examination precedes the test in every case

Several safety factors are built into the test The first two stages of the test are slow walking speeds allowing the subject to adapt to the exercise Any fear or anxiety with regard to the test is usually dissipated during this period Subjects with moderate or severe pulmonary or cardiac disease often stop at this point with symptoms referable to the underlying disease Unconditioned middle aged subjects or those with mild disease usually stop in the fourth stage or early in the fifth stage because their legs are tired from the progressive increase in work Only well-conditioned individuals and young athletes begin the seventh stage and extremely few finish the entire test since fatigue and dyspnea are usually pronounced at that point

In any test that attempts to measure

maximal performance motivation is a very important factor. To insure good performance the purposes and methods of performing the test were explained to each individual. The performance of this group was exceptionally good and motivation was questionable in only three instances. In the YMCA group there was keen competition among the active men to finish the entire test. The test itself is a check on motivation. In those subjects who stopped in the early stages for no obvious reason the maximal heart rates were less than 150 beats per minute. Duration of walking and maximal heart rate can be used to roughly assess motivation especially in normal subjects. In the age group 40 to 54 the mean maximal heart rate was 175 and the mean duration was 90 seconds of the fifth stage. In the youngest age groups the mean maximal heart rate was over 200 and in the oldest groups it was 160.

The value of the electrocardiogram during exercise as well as after exercise has been the subject of recent reports. Bellet reports that 4 of 18 normal subjects with positive bicycle ergometer tests would have been missed if only the postexercise tracings had been taken. In this study all the tracings in which evidence of myocardial ischemia was apparent during exercise revealed myocardial ischemia after exercise as well. The tracing taken immediately after the end of the test has been the most sensitive one for detecting myocardial ischemia. Usually this ischemic segmental S-T depression disappeared within 30 seconds after the test but in 1 case it persisted 15½ minutes before returning to normal. In 2 cases the tracings during exercise and those in the first 3 minutes after exercise were normal but tracings taken 5 minutes or more after the test showed definite myocardial ischemia.

To date the study demonstrates that graded maximal exercise testing is quite practical for men of all ages and body weights. Men of all degrees of physical conditioning can be evaluated. If future examinations of the men who have exhibited these ECG abnormalities reveal a high incidence of clinical coronary heart disease the reliability, specificity, and predictive value of the multistage exercise capacity test will be established.

Summary

A study of 433 asymptomatic men emphasizes the value of strenuous exercise testing in the early detection of myocardial ischemia. The sensitivity of the maximal exercise capacity test was nine times greater than that of the double Master's two-step test in eliciting electrocardiographic evidence of myocardial ischemia in 201 normal men who were over 34 years of age. Improved detection of potential coronary heart disease by this method is illustrated by comparison with several epidemiologic studies. If the reliability and specificity of this electrocardiographic abnormality in predicting clinical coronary heart disease is confirmed by future follow-up examinations a method of detection and study of potential coronary heart disease and factors influencing its course will be available.

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The masking of aortic stenosis by mitral stenosis

*R. S. Zitnik, M.D.**
*T. E. Piemme, M.D.***
*R. J. Messer, M.D.***
*D. P. Reed, M.D.***
F. W. Haynes, Ph.D.
L. Dexter, M.D.
Boston, Mass.

As cardiovascular surgery progresses, the open-heart repair of diseased mitral and aortic valves, with the replacement of one or both valves simultaneously, is being done more frequently.[1] However, the operation of choice for mitral stenosis is still closed mitral valvuloplasty when there is not significant involvement of other valves, heavy calcification of the mitral valve, or regurgitation, because good results can be obtained at a decidedly lower risk than with open-heart surgery and valve replacement.[2]

When a patient presents with the signs and symptoms of tight mitral stenosis and has in addition a murmur suggestive of aortic stenosis, the clinician must determine the severity of the aortic lesion if the additional risks of open-heart surgery are to be avoided. This communication is concerned with the problem of assessing severe mitral and aortic stenosis when both coexist.

Methods

In a selected series of 150 patients with combined mitral and aortic valve disease who were studied by means of catheterization of the right and left sides of the heart, 10 were found to have severe combined mitral stenosis and aortic stenosis *without hemodynamically significant regurgitation at either valve*. These findings were confirmed by surgery in each case. An additional 10 patients with only tight mitral stenosis and 10 patients with tight aortic stenosis[3] were also compared to this group.

All patients were personally examined by one of us (L. D.). Heart murmurs were graded on a basis of 1 to 6.[4] Standard 12 lead electrocardiograms were taken on all patients and analyzed according to the criteria outlined by Levine.[5] Cardiac fluoroscopy was performed on all patients, and x-ray films were taken in the postero-anterior, lateral, and left and right anterior oblique positions. The size of the

From the Department of Medicine and Radiology, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Mass.

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*Postdoctoral Research Fellow, National Heart Institute, United States Public Health Service. Present address: Department of Medicine, Northwestern University Medical School, 303 East Chicago Ave., Chicago, Ill. 60611.

**Research Fellow, American Heart Association.

***Resident in Radiology, Peter Bent Brigham Hospital.

heart was graded from 0 (normal) to +4 (massive enlargement)

Catheterization of the left side of the heart was performed either by means of the posterior transthoracic route[7] or the transseptal technique[8] Cardiac outputs were determined by either standard Fick procedures or by the standard indicator dilution technique using radioactive I^{131} or indocyanine green dye as previously described[9] Phasic and mean pressures were recorded using Statham P23D strain gauge manometers All physiologic data were recorded photographically on an Electronics for Medicine electron beam recorder

Resistances were calculated in dynes sec cm $^{-5}$ by means of the standard modification of the Poiseuille equation The time tension index was calculated by means of the equation mean left ventricular systolic pressure × pulse rate × systolic ejection period[10] Valve areas were calculated according to the method of Gorlin and Gorlin[11] Systolic ejection periods were measured from the brachial arterial pressure pulse Predicted systolic ejection periods were obtained from the formula

$$\frac{2\ 3}{\sqrt{\text{heart rate}}}$$

Results

The symptomatology of this group of 10 patients was in general that of mitral stenosis (Table I Figs 1 and 2) There were 8 females and 2 males Eight had a history of previous rheumatic fever All had dyspnea on exertion Seven patients had orthopnea whereas 6 had paroxysmal nocturnal dyspnea One half of the subjects had peripheral edema at some time prior to their examination Only 3 had hemoptysis Angina pectoris was present in 4 of the 10 patients and syncopal episodes were experienced by 2 of these same individuals

Physical examination revealed only 2 patients with distended neck veins Three had the type of apex impulse usually associated with left ventricular hypertrophy Nine of the 10 had some carotid pulse abnormality (e g carotid shudder an anacrotic pulse or pulsus parvus et tardus)

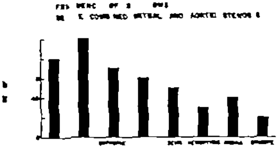


Fig 1 The frequency of symptoms in patients with severe combined mitral and aortic stenosis A R F Acute rheumatic fever in the past D O E Dyspnea on exertion P N D Paroxysmal nocturnal dyspnea All patients had symptoms commonly found in mitral stenosis whereas less than 40 per cent had symptoms typical of aortic stenosis

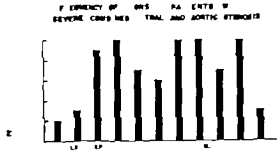


Fig 2 The frequency of signs in patients with severe combined mitral and aortic stenosis N V D Distention of neck veins L V A I Left ventricular apex impulse C P Carotid pulse abnormality (e g parvus et tardus or anacrotic pulse) M Mitral component of the first heart sound A Aortic component of the second heart sound O S Opening snap A S M Aortic systolic murmur A D M Aortic diastolic murmur M S M Mitral systolic murmur M D M Mitral diastolic murmur A F Atrial fibrillation All patients had the signs of mitral stenosis All had a murmur of aortic stenosis and 90 per cent had some abnormality of the carotid pulse on palpation Very few showed evidence of left ventricular hypertrophy on physical examination

All patients had a loud snapping mitral first heart sound and 6 had an opening snap in addition Seven had decreased or absent aortic second sounds All had murmurs of aortic stenosis aortic insufficiency and mitral stenosis whereas 7 had an additional murmur of mitral insufficiency There was no other clinical evidence of insufficiency at either the aortic or the mitral valve

Table I Signs and symptoms

Patient	Sex	Age (yr)	Previous rheumatic fever	Dyspnea on exertion	Orthopnea	Paroxysmal nocturnal dyspnea	Peripheral edema	Hemoptysis	Angina	Syncope
1	F	36	0	+	+	+	+	0	0	0
2	F	39	+	+	0	0	+	0	0	0
3	F	41	+	+	0	0	+	0	0	0
4	F	41	+	+	+	+	+	+	0	0
5	M	44	0	+	0	0	0	+	0	0
6	F	39	+	+	+	+	+	0	+	+
7	F	34	+	+	+	+	0	+	+	0
8	M	55	+	+	+	+	0	0	+	0
9	F	47	+	+	+	+	0	0	+	+
10	F	39	+	+	+	0	+	0	0	0
8F and 2M		41 5								
Per cent			80	100	70	60	60	30	40	20

+ Present 0 Absent N Normal ↑ Increase ↓ Decrease A aortic [illegible] (+ = present) S First

Table IIA Electrocardiographic analysis

Patient	Rhythm	Axis (degrees)	P R interval (sec)	RA hypertrophy	LA hypertrophy	RV hypertrophy	LV hypertrophy
1	NSR	70	0 16	0	+	0	0
2	NSR	85	0 16	0	+	0	0
3	NSR	55	0 22	+	+	0	0
4	NSR	40	0 22	+	+	0	+
5	NSR	80	0 21	+	+	+	0
6	NSR	85	0 18	0	+	0	+
7	NSR	80	0 20	0	+	+	0
8	AF	55	—	–	–	0	0
9	AF	90	—	–	–	+	+
10	AF	90	—	–	–	+	0
7NSR 3AF		73	0 19	3+	7+	4+	3+

NSR Normal sinus rhythm AF Atrial fibrillation RA and LA Right and left atrial RV and LV Right and left ventricular + Present 0 Absent

Analyses of the electrocardiograms (ECG) showed a normal sinus rhythm (NSR) in 7 and atrial fibrillation in 3 (Table IIA) The mean electrical axis was +73 degrees (range +40 to +90) The P R interval averaged 0 19 second (range 0 16 to 0 22) Three ECG showed right atrial hypertrophy whereas all 7 with NSR showed left atrial hypertrophy Right ventricular hypertrophy was present in only 4 ECG Three ECG showed evidence of left ventricular hypertrophy

The over all heart size radiographically was increased an average of 35 per cent (range +20 to +60) (Table IIB) All subjects showed left atrial and right ventricular enlargement Nine showed left ventricular enlargement of some degree Poststenotic dilatation of the aorta was present in 4 patients but all had a normal aortic knob Calcification of the aortic valve was observed in 3 subjects and calcification of the mitral valve in 5 The pulmonary artery and pulmonary vascular markings were increased in 7

Cardiac catheterization (Table III) revealed the average cardiac output to be low 3 1 L per minute (range 1 9 to 4 0)

Neck vein distention	LV apex impulse	Carotid pulse	S	S_2 A	S_2 P	Aortic systolic murmur	Aortic diastolic murmur	Apical systolic murmur	Apical diastolic murmur	Opening snap
0	0	+	↑	↓	↘	4	2	2	4	+
0	0	+	↑	↘	↘	3	1	2	2	+
0	0	+	↑	↓	↘	3	2	2	2	+
0	0	+	↑	↘	↘	2	2		1	0
0	+	+	↑	↘	↘	?	0		?	+
0	+	+	↑	↓	↘	4	2	0	?	+
0	0	0	↑	↓	↑	4	3	0	3	0
0	0	+	↑	↓	↘	3	2	0	1	0
+	+	+	↑	↓	↘	3		3	3	+
+	0	+	↑	↓	↑	2	2	2	?	0
20	30	90	100	0	20	100	90	0	100	60

heart sound. S_2 Second heart sound. A Aortic. P Pulmonary. LV Left ventricular

Table IIB X ray analysis

Patient	Over-all heart size (%)	LA enlargement	LV enlargement	RV enlargement	Pulmonary artery	Pulmonary vascular markings	Aortic root abnormality	Aortic valve	Mitral valve
1	+40	+3	+2	+3	0	+1	0	0	0
2	+25	+1	+1	+2	+1	0	0	+	0
3	+30	+2	+2	+3	+?	+3	0	0	+
4	+20	+1	+1	+2	0	+1	+1	0	0
5	+47	+2	+	+2	+1	+2	+?	0	+
6	+27	+?	+2	+2	+1	+1	0	0	+
7	+26	+1	0	+1	+1	0	0	+	+
8	+20	+2	+1	+2	+1	+	+2	+	+
9	+60	+2	+2	+3	0	0	0	0	0
10	+50	+2	+	+2	+2	+3	+?	0	0
	+35	10+	9+	10+	7+	[illegible]	4+	3+	5+

Poststenotic dilatation of aorta enlargement
[illegible] 0 (normal) to +4 (maximal). LA, LV, and RV Left atrial, left ventricular, and right ventricular

the cardiac index was 1 9 L per minute per square meter (range 1 3 to 2 4) Brachial arterial pressures were in the normal to low range except in one case with an average pressure of 126/76 mm Hg (range 98 to 176/62 to 104) mean systolic pressure was 94 mm Hg (range 75 to 125) The systolic ejection periods as measured from the brachial arterial pulse averaged 0 28 second (range 0 24 to 0 37) and were prolonged in all cases beyond the predicted ejection periods which averaged 0 25 second (range 0 21 to 0 27) (Fig 4)

Left ventricular mean systolic pressures averaged 173 mm Hg (range 130 to 222) whereas the end-diastolic pressure averaged 8 mm Hg (range −7 to +15) Left ventricular mean diastolic pressures averaged 5 mm Hg (range −9 to +9) whereas mean left atrial pressures were 22 mm Hg (range 12 to 28) The transmitral valve diastolic pressure difference was 16 mm Hg (range 8 to 28) The transaortic valve systolic pressure difference was 40 mm Hg (range 11 to 63)

The average mitral valve area in this

Table III Catheterization data

Patient	CO (L/min)	CI (L/min/M²)	BA pressure (mm Hg) S	BA pressure D	BA pressure SM	SEP (sec/beat)	Pulse rate (per min)	SU (sec/beat)	LV pressure (mm Hg) SM	LV pressure ED	LV pressure MD	Mean LA pressure (mm Hg)
Group I—MS and AS												
1 A.R.	3 1	1 4	1[illegible]	6	94	0 [illegible]	91	0 08	130	10	8	27
C C	0	1 5	133	77	96	0 26	83		206	7	4	17
3 M.S.	4 0	4	95	6[illegible]	[illegible]	0 7	85	0 20	145	6	5	20
4 F.M.	3 3	3	133	90	106	0 30	85	0 21	155	9	6	15
5 B.O.	2	1 5	1 6	104	1	0 30	77		196	8	6	23
6 G.A.	3 6	4	1.3	9	100	0 23	100		222	9	9	25
7 V.E.	3 5		101	0	84	0 4	108	0 1	15	—7	—9	19
8 J.G.	3 6	1 9	133	65	90	0 3	64	0 19	181	15	9	23
9 N.G.	3	1 5	11	77	90	0 26	125	0 18	1 0	8	6	27
10 L.F.	1 9	1 3	114	60	84	0 31	73	0	136	1	3	23
Average	3 1	1 9	1 6	76	94	0 28	83	0 17	173	5	6	22
Range (1 9 to 4 0)		(1 3 4)	(95-1 6)	(60 104)	(75-1 6)	(0 4-0.37)	(64-125)	(0 08-0 2)	(130-222)	((—7)-15)	((—9)-9)	(1 25)
Group II—AS												
3		3 9			93	0 25	120		175	7		
4		6			125	0	136		278	20		
		9			90	0 31	81		180	14		
		4 9			103	0 30	93		222	22		
		4 1			1 0	0 26	107		190	10		
		3			106	0 22	100		164	6		
		6			105	0 6	85		158	18		
		3 4			90	0 23	7		154	4		
11		4 8			90	0 4	106		149	3		
12		3 9			135	0 23	104		1 0	6		
Average		4 1			105	0 6	100		18	1		
Range		(2 6- 6)			(83 135)	(0 2-0 31)	(136)		(149-278)	(3-2)		
Group III—MS												
1 L.R.		1 6			103	0 23	80		103	11		22
2 J.R.		9			5	0 23	94		5	0		16
3 S.B.		1 9			95	0 29	6		9	7		16
4 R.D.		1 9			88	0 25	4		85	6		23
5 H.C.		5			90	0 24	67		90	10		20
6 M.M.		3 1			107	0 25	6		107	3		18
7 J.F.		9			81	0 26	90		81	5		21
8 P.O.		1 3			91	0 2	100		91	1		30
9 J.M.		1			71	0 4	65		71	1		4
10 O.C.		1 9			95	0 4	97		95	3		23
Average		2			89	0 27	—		89	7		22
Range		(1 6-2 9)			(71 107)	(0.22-0.29)	(6 100)		(71 107)	(0-1)		(16-30)

Femoral artery
†Diastolic mean
Patient number in Reference 4
CO Cardiac output CI Cardiac index BA Brachial arterial LV Left ventricular (ventricle) LA Left atrial PA Pulmonary arterial ... ED End-diastolic MD Mid-diastolic MS Mean systolic ... Aortic stenosis SEP Systolic ejection period SU Systolic upstroke

PA pressure (mm Hg) S	PA pressure (mm Hg) D	PA pressure (mm Hg) M	RV pressure (mm Hg) S	RV pressure (mm Hg) ED	Mean RA pressure (mm Hg)	MS aortic valve gradient (mm Hg)	MD mitral valve gradient (mm Hg)	Calculated aortic valve area (cm²)	Calculated mitral valve area (cm²)	TTI of LV	Total systemic resistance (dyne sec cm⁻⁵)	Total pulmonary resistance (dyne sec cm⁻⁵)
—	—	—	—	—	—	11	19	0 7	0 8	[illegible]40	470	—
—	—	—	—	—	—	49	8	0 4	0 9	3 540	670	—
30	1	25	33	5	8	41	15	0 4	0 9	3 330	1 500	[illegible]
—	—	—	—	—	—	45	9	0 4	1 2	4 390	870	—
[illegible]	[illegible]	43	[illegible]	8	[illegible]	25	17	0 6	0	4 000	3 340	1 700
48	35	40	—	—		65	14	0 4	0 9	3 070	2 220	[illegible]90
49	22	37	45	4	4	43	25	0 8	0 6	3 630	1 970	850
67	77	41	6	[illegible]	[illegible]	63	19	0 5	0	3 840	010	910
—	—	—	—	—	—	47	1	0 3	0 6	4 690	3 130	—
[illegible]	47	63	86	11	[illegible]	71	1	0 4	0	3 360	3 400	600
57	31	4	50	6	7	40	16	0 5	0 8	3 730	5[illegible]0	1 170
([illegible]-98)	([illegible]-47)	(25-63)	(30-86)	(4-17)	(4-9)	(11-63)	(5-25)	(0 3-0 [illegible])	(0 5-1 [illegible])	([illegible])	([illegible]-3,340)	([illegible]-2,000)
								0 3		5 230		
								0 4		19 710		
								0 4		4 020		
								0 4		3 400		
								0 5		4 040		
								0 5		3 610		
								0 6		3 900		
								0 6		3 110		
								0 6		6 720		
								0 7		4 470		
								0 5		5 110		
								(0 3-0 7)		(3 110-10 [illegible])		
									0 5	2 300		
									0 8	1 [illegible]60		
									0 8	[illegible]090		
									0 6	1 630		
									1 0	1 500		
									1 0	[illegible]110		
									1 1	1 910		
									0 6	[illegible]370		
									0 6	1 730		
									0 6	1 850		
									0 8	1 930		
									(0 6-1 1)	(1,500- [illegible])		

Right [illegible] ventricular. RA Right atrial. TTI Time [illegible] index. S Systolic. D Diastolic. M Mean. SM Systolic mean. MS [illegible] [illegible] systemic resistance. Pulm [illegible] Pulmonary resistance.

series was calculated to be 0.6 square centimeter (range 0.5 to 1.2). The average aortic valve area was by calculation 0.5 square centimeter (range 0.3 to 0.7).

Whenever recorded, pulmonary arterial pressures were high, with systolic pressures averaging 57 mm. Hg (range 33 to 86) and diastolic pressures averaging 42 mm. Hg (range 25 to 63). Right ventricular end-diastolic pressures averaged 8 mm. Hg (range 4 to 12), whereas the average right atrial pressure was 7 mm. Hg (range 4 to 9).

Time tension indices for the left ventricle were above the normal range, averaging 3,730 (range 2,360 to 5,020). In most cases the total systemic vascular resistance was elevated, averaging 2,550 dynes sec. cm.⁻⁵ (range 1,500 to 3,540), associated with the reduced cardiac output. In all cases in which the pulmonary arterial pressure was measured, total pulmonary resistance was also elevated, averaging 1,170 dynes sec. cm.⁻⁵ (range 500 to 2,600).

Discussion

All patients had unequivocal signs and symptoms of mitral stenosis (Figs. 1 and 2). Contrary to previous reports[1,13] the first heart sound was loud and snapping in all cases. Six patients also had opening snaps of the mitral valve. All x-ray films showed left atrial enlargement, and there was electrocardiographic evidence of this in all those with normal sinus rhythm. Right ventricular enlargement was seen on every x-ray film, but right ventricular hypertrophy was observed by ECG in only 4 cases. There was also some disparity on x-ray examination between the large size of the left atrium and right ventricle and the smaller than expected size of the pulmonary artery (Table II), although some degree of pulmonary hypertension was present in all cases in which the pulmonary arterial pressure was measured (Table III).

In addition to the evidence of mitral stenosis, all patients had some other signs and symptoms of aortic stenosis as well as an ejection type of murmur in the aortic area. Four had angina pectoris, and 2 of these had syncopal episodes. Nine of the 10 had some abnormality of the carotid pulse (e.g., anacrotic or parvus et tardus pulse). Left ventricular enlargement was present radiologically in 9 of the 10 patients, but the ECG pattern of left ventricular hypertrophy was present in only 3 of these. Other x-ray evidence of aortic stenosis was calcification of the aortic valve in 3 patients and poststenotic dilatation of the ascending aorta in 4. In Patient No. 7 there was no x-ray or ECG evidence of left ventricular hypertrophy, but calcification of the aortic valve and the presence of angina pectoris suggested a significant degree of aortic stenosis.

The electrocardiogram was particularly disappointing as a guide to the presence of severe aortic stenosis in the presence of mitral stenosis.[13,14] A large percentage of the patients (7 of the 10) had normal sinus rhythm, as had been reported previously.[14] None had left axis deviation. Only 3 ECG revealed evidence of left ventricular hypertrophy. In each of these 3 cases angina pectoris was also present. Each of these patients also had a time tension index (TTI) which was elevated not only above the normal range but also above the mean for this group (Fig. 3). This increase in the TTI was largely due to a prolongation of the systolic ejection period of the left ventricle (Fig. 4).

Since the TTI has a relation to the total effort of the left ventricle in terms of oxy

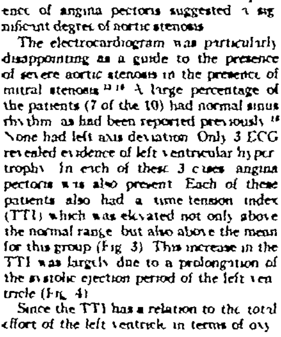


Fig. 3. The relationship of x-ray evidence of left ventricular hypertrophy to the time tension index, to ECG evidence of left ventricular hypertrophy, and to the occurrence of angina pectoris. There is no evident relationship between x-ray size and left ventricular stress as measured by the time tension index. However, there is a relationship between ECG evidence of left ventricular hypertrophy, angina pectoris, and the time tension index, which suggests that these features connote severe left ventricular stress.

gen consumption[16] the presence of left ventricular hypertrophy on the ECG suggests a higher degree of stress on the left ventricle in these patients than in the group as a whole. Any significant degree of mitral or aortic insufficiency would obviate the importance of this feature.

In our experience whenever a patient with tight mitral stenosis presents with any sign or symptom of aortic stenosis in addition to an aortic ejection type of murmur, severe aortic stenosis cannot be ruled out. The absence of any particular sign or symptom of aortic stenosis does not exclude its presence. However, we have not encountered a patient with severe mitral stenosis in whom the *only* evidence of tight aortic stenosis was an aortic ejection type of murmur.

The difficulty of quantifying the severity of aortic stenosis in the presence of severe mitral stenosis has been recognized previously.[1, 17] Fig. 5 compares the circulatory findings in pure mitral stenosis, pure aortic stenosis,[4] and combined severe aortic and mitral stenosis in cases in which the calculated mitral and aortic valve areas were matched so as to be practically identical. The low cardiac output in the cases of combined lesion is clearly attributable to the mitral rather than to the aortic stenosis. Indeed, in pure aortic stenosis the cardiac output remains normal or even somewhat high until decompensation of the left ventricle occurs,[4] at which time end-diastolic pressure rises and cardiac output falls. Since for any given aortic valve size there is a direct relationship between the amount of pressure that is generated by the left ventricle and the cardiac output,[5] the decrease in blood flow with the mixed lesion allows a decrease in left ventricular systolic pressure as shown in Fig. 5 and hence a decrease in total left ventricular work. Thus the total stress on the left ventricle as indicated by the TTI was less than expected for pure aortic stenosis with a normal cardiac output. It is believed that this reduction in output is the basic cause of inconstancy of symptoms and signs of aortic stenosis in patients with the mixed lesion.[12]

Differences in mean systolic pressure across the aortic valve ranged from 11 to 63 mm Hg, as shown in Table III. Some

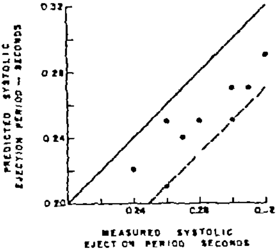


Fig. 4. The relationship of the predicted systolic ejection period to the systolic ejection period measured from the brachial artery. The systolic ejection period was prolonged above the predicted value in all subjects but markedly so (over .25 seconds per minute) in those with ECG evidence of left ventricular hypertrophy (*solid dots*).

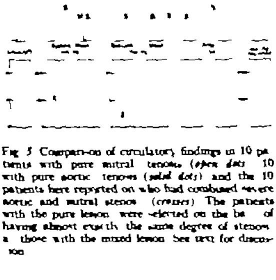


Fig. 5. Comparison of circulatory findings in 10 patients with pure mitral stenosis (*open dots*), 10 with pure aortic stenosis (*solid dots*), and the 10 patients here reported on who had combined severe aortic and mitral stenosis (*crosses*). The patients with the pure lesion were selected on the basis of having almost exactly the same degree of stenosis as those with the mixed lesion. See text for discussion.

of these differences were in the insignificant range if cardiac output had not been taken into consideration. Only the simultaneous measurement of pressure and flow allows a true appreciation of valve size.

The conclusion is that catheterization of the left side of the heart should be performed prior to operation in all patients with severe mitral stenosis in whom a murmur and at least some one other sign or symptom of aortic stenosis is present. Once serious suspicion of aortic stenosis has been raised, this is the only

our experience to quantify the severity of this lesion prior to operation

Summary

The clinical data (signs and symptoms x ray and electrocardiographic analysis) and hemodynamic findings in 10 patients with severe mitral and aortic stenosis have been presented

All patients had signs symptoms and radiologic stigmata of mitral stenosis Normal sinus rhythm was present in 7 of the 10 patients and right ventricular hypertrophy in only 3 Many of the features usually considered to be a sine qua non of severe aortic stenosis were absent in these cases However all patients had at least one manifestation other than the typical murmur of aortic stenosis (e g angina syncope abnormal carotid pulse left ventricular enlargement by x ray or ECG examination calcification of the aortic valve or dilatation of the aortic root)

All patients with ECG evidence of left ventricular hypertrophy also had angina and significantly elevated time tension indices This was due largely to prolongation of the systolic ejection period It is suggested that ECG evidence of left ventricular hypertrophy in this clinical setting without significant mitral or aortic regurgitation signifies severe left ventricular stress and severe aortic stenosis

A decrease in cardiac output secondary to mitral stenosis reduces the differences in pressure across the aortic valve and therefore reduces the total left ventricular stress as reflected by the time tension index It is believed that this reduction in output is the basic cause of inconstancy of symptoms and signs of aortic stenosis in patients with tight mitral and aortic stenosis

When aortic stenosis is suspected in patients with severe mitral stenosis the only certain method of quantitative evaluation is catheterization of the left side of the heart with simultaneous measurement of transvalvular pressure differences and blood flow

We wish to express our appreciation to Dr Dwight E Harken and Dr Harrison Black for the privilege of studying some of their patients and for furnishing the surgical correlation of the clinical data

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The electrocardiogram in complete transposition of the great vessels

*Homobono B. Calleja, M.D.**
*Don M. Hosier, M.D.***
*Maria Z. Grajo, M.D.****
Columbus, Ohio

The electrocardiographic pattern in complete transposition of the great vessels has been described by some authors[1-4] as indicating right ventricular hypertrophy. Campbell and Suzman[5] and Astley and Parsons[2] state that the electrocardiogram is indistinguishable from that of tetralogy of Fallot. Others like Miller and associates have pointed out that the left ventricular hypertrophy pattern can occur even in the absence of an associated tricuspid atresia. Repeated electrocardiograms in an 18 year old boy reported on by Pung and associates[6] showed left ventricular preponderance. Keith, Rowe and Vlad[7] state that right ventricular hypertrophy occurs in only 32 per cent and combined ventricular hypertrophy in 25 per cent of all cases of complete transposition of the great vessels.†

In view of these conflicting opinions we reviewed the electrocardiograms of our previous series of cases of complete transposition of the great vessels (Table I). This report presents the different electrocardiographic expressions found in 53 cases.

Material and method

The cases of complete transposition of the great vessels in this study are limited to those in which the aorta and the pulmonary artery arise exclusively from the ventricle opposite to where they normally arise. Other anomalies in the origin of the aorta and the pulmonary artery from the right ventricle, Taussig-Bing complex, the so-called "corrected transposition," and

Table I. Cases of complete transposition of the great vessels seen at Children's Hospital, Columbus, Ohio (1953 to March 1960 inclusive)

Autopsy diagnosis	42
Angiocardiographic or cineangiocardiographic diagnosis	17
Clinical diagnosis	8
Total	67
Total number of cases with complete ECG, autopsy and/or angiocardiogram	53
(Excluded were 2 with dextrocardia and 1 with WPW syndrome)	

F[illegible] the K[illegible]d[illegible] Key Heart Laboratory, Children's Hospital, Ohio State University Health Center, Columbus, Ohio.
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Received for publication March 26, 1964.
*D[illegible] American Heart Ch[illegible] [illegible] C[illegible]ty [illegible] Medical C[illegible] [illegible] Professor [illegible] Department of Medicine, Faculty of Medicine, University of [illegible] Manila, Philippines. Address: Am[illegible] Heart Ch[illegible] 316 Quezon [illegible] P.O. Box 1054 Manila, Philippines.
**[illegible] Professor of Pediatrics (Cardiology), Ohio State University Health Center, Columbus, Ohio.
***[illegible] Cardiology Department of Medicine and of Pediatric Cardiology, Faculty of Medicine, University of [illegible] Manila, Philippines.
†[illegible] pulmonary artery [illegible] Cases [illegible] pulmonary artery [illegible] 75 per [illegible] of the cases of [illegible] hypert[illegible]

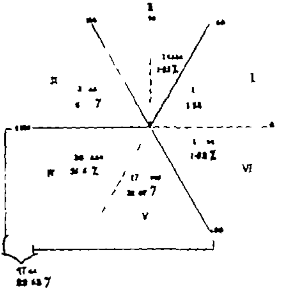


Fig 1 Distribution of the ÂQRS in Bayley's triaxial system

overriding of the aorta or the pulmonary artery are excluded Cases of transposition of the great vessels with single ventricle are included because the situation is analogous to a large ventricular septal defect in which the pressures in the right and left ventricles are the same hence clinically difficult to separate That complete transposition of the great vessels can be diagnosed with confidence at autopsy in spite of a single ventricle doubly underlines the importance of the anatomic relationship of the two great vessels to each other The presence of a single ventricle provides the much needed shunt for survival of the newborn infant To exclude these cases would be to commit a grave error of placing an associated defect over and above the more basic anomaly Eighty per cent of the cases of single ventricle have complete transposition of the great vessels[7] whereas only 6 per cent of the cases of complete transposition of the great vessels have single ventricle[8]

Complete electrocardiographic tracings including 3 bipolar limb leads 3 unipolar limb leads and 6 unipolar chest leads were available in 56 patients With one exception Lead V_{4R} was recorded in all patients Each electrocardiogram was analyzed with regard to the ÂQRS P P R interval R in Lead aVR Q in Lead V_{4R} and V_1 QRS complex in the right precordial leads T wave in the right and left precordial leads and the presence of right left or combined ventricular hypertrophy Two cases of dextrocardia and 1 case of Wolff Parkinson White syndrome were excluded from this study for obvious reasons

Electrocardiographic criteria

Mean electrical axis of the QRS The mean electrical axis of the QRS is determined by taking the area enclosed by the positive and negative deflections in the bipolar limb leads Normal axis = 0 degrees to +119 degrees right axis deviation (RAD) = +120 degrees through +180 degrees to −90 degrees left axis deviation (LAD) = 0 degrees to −89 degrees

P wave The P wave is considered to be tall if it is 3 mm or greater in Lead II or 2.5 mm or greater in any other lead Notching and peaking are noted The P wave is broad if it is 0.10 second or more in Lead II

P R interval A prolonged P R interval is present if it exceeds the normal for age and rate[9] prolongation by digitalis is ruled out by history

R′ in the right precordial leads R′ is the second positive deflection of the QRS complex with an unequivocal S wave preceding it

Incomplete right bundle branch block (IRBBB) An RSR′ pattern in the right precordial leads in which the QRS measures 0.11 second or less indicates incomplete RBBB

Right ventricular hypertrophy (*Table II*) There is definite right ventricular hypertrophy if a Q or upright T wave is present in the right precordial lead or if two or more criteria are met In patients under 1 month of age the R S ratio in the right precordial leads is excluded as a criterion An upright T wave in the right precordial leads is not used if it is clearly due to an inverted or diphasic T wave in Leads V_5 or V_6 because of left ventricular hypertrophy and or digitalis

Left ventricular hypertrophy (*Table II*) There is definite left ventricular hypertrophy if a left axis deviation of −30 degrees or ST T changes in Lead V_6 are present or if two or more criteria are satisfied Digitalis effect is excluded by history before the ST T changes are at

tributed to left ventricular hypertrophy. Furthermore this criterion is excluded if the S-T changes in the left precordial leads appear to be extensions of similar changes in the right precordial leads.

Combined ventricular hypertrophy Combined ventricular hypertrophy is present if the precordial leads show evidence suggestive of both right and left ventricular hypertrophy.

Results

Mean electrical axis Fig. 1 shows the distribution of the ÂQRS in Bayley's triaxial system. In 88.68 per cent of the patients the ÂQRS was found in sextants IV and V. In isolated cases in which the ÂQRS was in sextants I, II and VI the patients all had single ventricle. The patient with ÂQRS in sextant VI (Case 37) also had tricuspid atresia. Only 3 patients (5.66 per cent) had the ÂQRS in sextant III. The youngest in the latter group was 3 months old.

P wave and P-R interval The P wave was peaked in 9 patients (16.98 per cent) and notched in 7 (13.21 per cent). In 22 patients (41.51 per cent) the P was normal. Fifteen patients (28.30 per cent) had tall and peaked or notched P. The P-R interval was normal in all except 1, in whom it was prolonged. This patient (Case 35) had single ventricle with pulmonary stenosis. One patient was excluded from this study because of a Wolff-Parkinson-White syndrome.

R wave in Lead aV$_R$ In one half of the cases R was greater than 5 mm and the R/S or R/Q ratio was equal to or greater than 1.0.

Q wave in right precordial leads Seven patients (13.21 per cent) had a definite Q wave in Leads V$_{4R}$ and V$_1$. All were 3 months old or over. Two of them (Cases 7 and 50) had their ÂQRS in sextant III.

QRS complex in the right precordial leads (Table III) The pattern of RSR' in Lead V$_1$ with incomplete right bundle branch block (IRBBB) was present in 7 patients (13.21 per cent). There was no complete right bundle branch block. In 35 patients (66.04 per cent) an rs, rS, Rs or RS pattern was present. The small r and a variant (rs) alone was found in 29 patients (54.72 per cent). Tall R with no Q or S was seen in 2 patients (3.77 per cent) and in another 2 only a small r was present. The R was notched in 19 patients (35.85 per cent).

T wave in right and left precordial leads (Table III) Thirty patients (56.60 per cent) had an upright T wave in the right precordial leads. Seven of these had a diagnosis of left ventricular hypertrophy, 3 had combined ventricular hypertrophy, and 20 had right ventricular hypertrophy. Conversely, in 23 patients (43.40 per cent) the T wave in the left chest leads was diphasic (17) or inverted (6). There were 10 patients with right ventricular hypertrophy, 7 with left ventricular hypertrophy, and 4 with combined ventricular hyper-

Table II Electrocardiographic criteria

Right ventricular hypertrophy
1. Electrical axis +120 degrees or greater
2. P wave 3 mm or greater in Lead II or 2.5 mm or greater in any other lead
3. R/S or R/Q ratio in Lead V$_{4R}$ greater than 1.0
4. Q wave in Leads V$_{4R}$ and V
5. R in Lead V$_{4R}$ or Lead V is 10 mm or greater with no S wave
6. R' in the right precordial leads greater than 10 mm in the presence of IRBBB
7. R/S ratio Lead V greater than and R/S ratio in Lead V less than those shown below

	1-3 mo	4-11 mo	1-2 y	3-5 yr	6-15 yr
R/S in V$_1$	7.0	4.5	2.5	2.0	1.5
R/S in V$_6$	0.5	0.7	0.8	0.9	0.9

8. T wave in Lead V$_{4R}$ or Lead V upright after 24 hours
9. Depressed S-T and diphasic or inverted wave extending from Lead V or Lead V

Left ventricular hypertrophy
1. Electrical axis greater than −30 degrees
2. R in Lead I plus S in Lead III exceeds 30 mm
3. R in Leads II and III exceed 45 mm
4. R in Lead aV$_L$ or Lead aV exceed 20 mm
5. R in Lead V exceed 30 mm in infants 1 to 3 years old or over 25 mm in subjects 3 years old or over
6. Onset of intrinsicoid deflection in Lead V exceeds 0.04 second
7. Depressed S-T and inverted T wave in Lead V$_6$ with or without increased voltage
8. The sum of R in Lead V or Lead V plus S in Lead V or Lead V$_1$ exceeds 35 mm

Table III

Patient	Age	QRS_{V_1}	T_{V_1}	T_{V_6}	ECG diagnosis
A TGV with single shunts					
With VSD					
1 R H	4 days	rs	Upright	Diphasic	RVH
2 B B	6 wk	rsR	Diphasic	Diphasic	RVH
3 J W	3 mo	qR	Inverted	Upright	RVH
4 T B	3 mo	rs	Upright	Upright	RVH
5 J R	3 mo	RS	Upright	Inverted	CVH
6 T W	4 mo	rsR	Diphasic	Upright	RVH
7 E B	5 mo	qRs	Upright –	Upright	RVH
8 T R	7 mo	rsr	Diphasic	Upright	CVH
9 M M	11 mo	R	Upright	Upright	RVH
With PDA					
10 B S	? days	rs	Diphasic	Diphasic	N
11 B W	2 days	rs	Inverted	Upright	N
12 F G	2 wk	rs	Upright –	Upright	RVH
13 K M	1 mo	rs	Upright	Diphasic	RVH
With ASD					
14 M G	18 da	rs	Diphasic	Upright	RVH
15 T B	4 mo	rs	Diphasic	Upright	RVH
B TGV with multiple shunts					
With VSD and PDA					
16 D K	2 days	r	Upright –	Upright	RVH
17 K T	4 days	rs	Diphasic	Upright	N
18 F C	7 wk	rs	Diphasic	Diphasic	LVH
19 M M	10 wk	rs	Upright	Inverted	RVH
With VSD and ASD					
20 R L	1 mo	rs	Diphasic	Upright	N
21 H L	10 wk	rs	Upright	Diphasic	RVH
22 K M	11 mo	rs	Upright	Diphasic	RVH
With VSD PDA and ASD					
23 K L	7 days	rs	Upright –	Upright	RVH
24 S O	1 mo	rR	Upright	Diphasic	RVH
25 J H	5 wk	rs	Upright	Inverted	LVH
With PDA and ASD					
26 J B	2 days	rsr	Upright	Inverted	LVH
27 C C	2 days	rs	Flat	Upright	N
28 T D	3 days	r	Inverted	Upright	N
29 C C	5 days	R	Upright –	Upright	RVH
30 J A	2 wk	rs	Upright	Upright	RVH
31 W R	19 days	Rs	Diphasic	Diphasic	RVH
32 R C	21 days	rs	Diphasic	Diphasic	N
33 D R	8 wk	rs	Upright –	Upright	RVH

A [?] associated with pulmonary stenosis.
TGV Transposition of the great vessels; VSD Ventricular septal defect; PDA [illegible] ductus arteriosus; ASD [illegible] septal defect.
RVH LVH CVH Right left and combined ventricular hypertrophy respectively. N Normal.
T [illegible] III [illegible] on page 35

trophy Two patients (Cases 10 and 32) who had diphasic T waves in Leads V_5 $_6$ failed to meet the criteria for ventricular hypertrophy and hence were considered to be normal Both were under 1 month of age—7 days and 21 days old respectively In 8 patients the T wave was equally tall in the right and left precordial leads The T wave was low or notched in Leads V_5 $_6$ in 3 patients and in another 3 the T was taller than in the right precordial leads

Ventricular hypertrophy (*Table III*) Definite right ventricular hypertrophy was diagnosed in 33 patients (62 26 per cent) left ventricular hypertrophy in 8 (15 09 per cent) and combined ventricular hypertrophy in 5 (9 43 per cent) Four of the tracings which were interpreted as indicating left ventricular hypertrophy were from patients with single ventricle Seven patients (13 21 per cent) who had normal tracings were all under 1 month of age

Figs 2 3 4 and 5 are examples of a normal tracing and tracings showing right ventricular hypertrophy left ventricular hypertrophy and combined ventricular hypertrophy respectively

Five patients had associated pulmonary stenosis Of these 1 with ventricular septal defect showed right ventricular hypertrophy 1 with combined ventricular and atrial septal defects had a normal tracing and of 3 patients with single ventricle 2 had left ventricular hypertrophy and 1 had right ventricular hypertrophy

Discussion

The mean manifest electrical axis of the QRS was located in sextants IV and V in 88 68 per cent of the patients When one considers that the majority of these patients were under 1 year of age this orientation appears to fall within the normal range for the group The P wave was ab

Table III—Cont d

Patient	Age	QRS	T	T	ECG diagnosis
C TGV with single ventricle					
34 B B	2 day	rs	Upright	Diphasic	LVH
35 R M	7 day	rs	Diphasic	Diphasic	CVH
36 S M	10 day	rs	Upright	Upright	LVH
37 T D	5 mo	rS	Upright	Inverted	LVH
38 S H	2 yr	rs	Upright	Diphasic	LVH
39 R B	6 yr	qr	Inverted	Upright	RVH
D TGV with no apparent shunt at autopsy					
40 L L	4 mo	rs	Upright	Upright	RVH
E TGV with angiocardiograms (type and number of shunts not conclusive)					
41 K D	4 days	rs	Diphasic	Diphasic	RVH
42 E E	9 day	rs	Upright	Upright	RVH
43 R C	5 wk	rsr	Upright	Diphasic	RVH
44 L C	3 mo	rs	Upright	Upright	RVH
45 C A	5 mo	rS	Upright	Inverted	LVH
46 D S	5 mo	qR	Inverted	Upright	RVH
47 J M	8 mo	Rs	Inverted	Upright	RVH
48 D F	9 mo	rsR	Inverted	Upright	RVH
49 B P	13 mo	rS	Upright	Diphasic	CVH
50 L G	14 mo	qR	Inverted	Upright	RVH
51 D K	2 yr	rs	Upright	Upright	RVH
52 B C	3 y	qR	Inverted	Upright	RVH
53 W N	4 y	qrS	Upright	Diphasic	CVH

Table IV. Ventricular hypertrophy in 53 patients

Shunt: Number	Shunt: Type	*RVH*	*LVH*	*CVH*	*N*
Single	VSD	7		2	
	PDA	2			2
	ASD	2			
Multiple	VSD + PDA	2	1		1
	VSD + ASD	2			1
	VSD + PDA + ASD	2	1		
	PDA + ASD	4	1		3
Single ventricle		1	4	1	
No apparent shunt		1			
Type and number of shunt not conclusive by angiocardiography		*10*	*1*	*2*	
Total		33	8	5	7

Associated with pulmonary stenosis: VSD, 1; VSD and ASD, 1; Single ventricle, 1.
VSD, Ventricular septal defect; *PDA*, Patent ductus arteriosus; *ASD*, Atrial septal defect; *RVH*, *LVH*, *CVH*, Right, left, and combined ventricular hypertrophy, respectively; *N*, Normal.

normal in more than 50 per cent, but the P-R interval was normal in all except one. One patient with a Wolff-Parkinson-White syndrome was excluded from this study.

Except for an upright T wave after the first 24 hours of life in the right precordial leads and/or a Q wave in these leads, there were no reliable signs of right ventricular hypertrophy in the electrocardiogram in the first months of life. A recent vectorcardiographic study[9] reported definite diagnostic clues in this age group.

Seven patients who had a normal electrocardiogram were all under 1 month old. Measurement of the voltage of the R wave in the right precordial leads is unreliable because of its wide variation. For example, in none of these normal tracings did the voltage of R definitely exceed the maximum of 20 to 29 mm. in the right precordial leads for the first month of life. In fact, only 2 patients had a tall R in Lead V_1.

The dominant QRS pattern in Lead V_1 is that of the small r and s type. It was found in 29 patients (54.72 per cent). This pattern appeared regardless of age. A 2-year-old patient (Case 51) with a definite electrocardiographic diagnosis of right ventricular hypertrophy also showed a small r and s in Lead V_1. It is fortunate that an upright T in Lead V_1 is frequently associated with a normal voltage of R in the right precordial leads. In 29 patients with rs in Lead V_1, an upright T in the same lead facilitated the diagnosis of right ventricular hypertrophy in 14 (49.00 per cent).

Typical right ventricular hypertrophy pattern was found consistently in older patients. Marked right axis deviation and Q wave in the right precordial leads were seen only in patients who were 3 months old or older. Working against the normally higher systemic pressure, the right ventricle had to hypertrophy in order to overcome this resistance. The normal pattern of right ventricular atrophy after birth is nullified by the demands for increasing pressure work to meet systemic resistance. Normally, the right ventricle atrophies soon after birth and never regains its birth weight until the first year of life is reached. Conversely, the left ventricle increases rapidly in weight, and the normal adult weight relationship of the two ventricles is reached at the age of 6 months.[10]

Only 7 patients (13.21 per cent) had an r′ or R in Lead V_1. Two patients with atrial septal defect had a diagnosis of definite right ventricular hypertrophy without showing RSR pattern.

According to Keith and associates the electrocardiogram in patients with complete transposition of the great vessels shows right ventricular hypertrophy in 32 per cent and combined ventricular

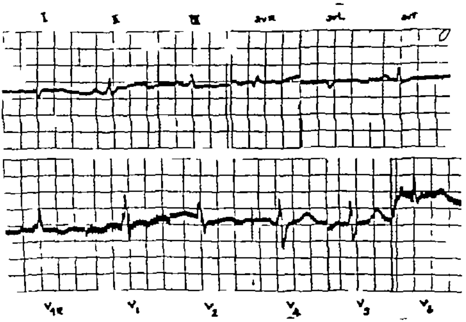


Fig. 2. Case 11. B.W., age 2 days. The electrocardiogram is within normal limits for age. T in V and R S T in V_{4-6} all appear normal at this age. At autopsy the left ventricle measured 6 mm and the right ventricle 3 mm. (ECG taken at a paper speed 50 mm per second.)

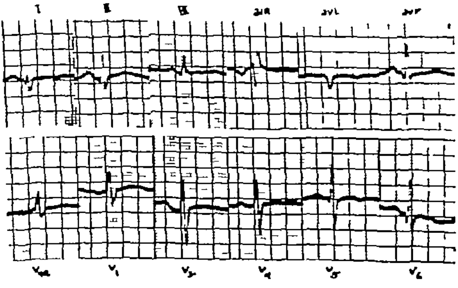


Fig. 3. Case 1. H.I., age 10 weeks. Right ventricular hypertrophy with juvenile T pattern in V. The T wave in V is upright. (ECG taken at paper speed of 50 mm per second.)

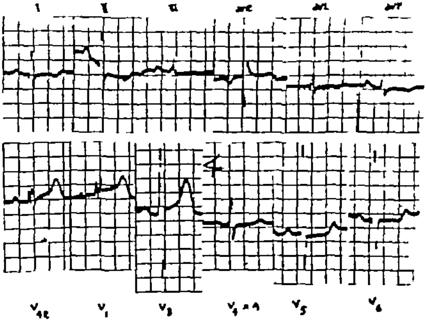


Fig. 4. Case 26. J. B., age 2 days. Left ventricular hypertrophy with tall R and ST-T change in V_6. T in V_{4R} and V_1 is upright and may indicate right ventricular hypertrophy. However, the upright T in the right precordial leads was interpreted as being reciprocal to the T change in V_6. Note the S wave in V_6 is not abnormal for this age. (ECG taken at a paper speed of 50 mm. per second.)

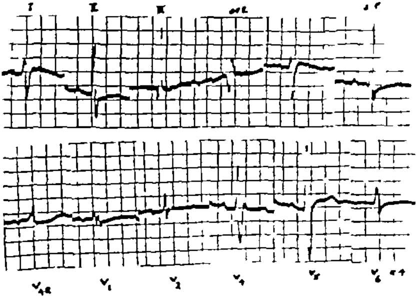


Fig. 5. Case 8. T. I., [illegible] month. Combined ventricular hypertrophy showing a tall R and deep S in V_6. The T wave in the right and left precordial leads is not remarkable. (ECG taken at a paper speed of 50 mm. per second.)

hypertrophy in 25 per cent and left ventricular hypertrophy occurs mostly in patients with tricuspid atresia and an overriding tricuspid valve. Excluding the cases of single ventricle with electrocardiographic diagnosis of left ventricular hypertrophy in 4, right ventricular hypertrophy in 1, and combined ventricular hypertrophy in 1, the corrected incidence in this series will be: RVH (32 patients)—68.08 per cent; LVH (4 patients)—8.51 per cent; CVH (4 patients)—8.51 per cent; and normal (7 patients)—14.89 per cent. The obvious discrepancy is due in part to the difference in the selection of patients included in the category "complete transposition of the great vessels" and in the electrocardiographic interpretation. (Keith and associates[7] consider the radiologic picture of the heart in making an electrocardiographic diagnosis.) The selection of electrocardiographic criteria of ventricular hypertrophy is also another cause for this disparity.

Zuckermann, Cisneros, and Novelo[11] studying only 3 cases of transposition of the great vessels concluded that the T wave in the left precordial leads is either low, flat, notched, or assumes the "juvenile" pattern. The latter occurs normally in the right precordial leads in the first year of life. It is described as a diphasic T wave with an initial convex negative deflection followed by a positive deflection. According to these authors, the anatomic characteristics of the right and left ventricles are reversed in transposition of the great vessels; hence, the juvenile T pattern is seen in the left precordial leads rather than in the right.

Analysis of the T waves in the precordial lead showed equal positivity in the right and left leads in 8 patients (15.09 per cent). In only 3 patients (5.66 per cent) was the T wave in Leads V_{5-6} low, flat, and/or notched, and in 3 other cases the T wave in these leads was actually taller than that in the right precordial leads. Seven patients (13.21 per cent) had a diphasic T wave in the left precordial leads in association with an upright T wave in the right precordial leads. Altogether, 10 patients (18.87 per cent) had electrocardiographic diagnoses of right ventricular hypertrophy with an upright T wave in the right precordial leads and a low, flat, notched, diphasic, or juvenile T pattern in Leads V_{5-6}. It should be noted, however, that this pattern may occur even when the left ventricle maintains a dimension thicker than that of the right ventricle. Actually, the diagnosis of right ventricular hypertrophy was made in 20 patients (37.72 per cent) with an upright T in Lead V_1 regardless of the morphology of the T in the left chest leads. Furthermore, 7 patients had a positive T wave in Lead V_1 but a diagnosis of left ventricular hypertrophy and 3 had a diagnosis of biventricular hypertrophy.

The electrocardiograms in the group with single ventricle showed 4 with left ventricular hypertrophy, and 1 each with right and combined ventricular hypertrophy. The high incidence of a left ventricular pattern as compared to either a right or combined ventricular hypertrophy pattern has good correlation with findings made recently by Van Praagh and associates in a morphologic study of single ventricle.

Summary

The electrocardiograms of 53 patients with complete transposition of the great vessels were analyzed. They showed the following:

1. In 68.68 per cent the ÂQRS was located in sextants IV and V of Bayley's triaxial system.

2. The P wave was normal in 41.51 per cent, tall and peaked or notched in 28.30 per cent, peaked in 16.98 per cent, and notched in 13.21 per cent.

3. The P-R interval was normal in 52 patients. It was prolonged in 1 with single ventricle and pulmonary stenosis.

4. An R in Lead aV_R was greater than 5 mm. and the R/S or R/Q ratio was greater than 1.0 in 50 per cent.

5. A Q wave in Leads V_{4R} and V_1 was present in 13.21 per cent. Both marked right axis deviation and a Q wave in the right precordial leads were absent in patients under 3 months of age.

6. An RSR' pattern in the right precordial leads was present in 13.21 per cent; an rs, rS, Rs, or RS was present in 66.04 per cent, of which rs alone constituted 54.72 per cent.

7. A low, notched, flat, diphasic, or

juvenile T wave in the left precordial leads was associated with right ventricular hypertrophy and upright T wave in the right chest leads in 18 87 per cent

8 Right ventricular hypertrophy (RVH) was diagnosed in 67 26 per cent left ventricular hypertrophy (LVH) in 15 09 per cent and combined ventricular hypertrophy (CVH) in 9 43 per cent and in 13 21 per cent the electrocardiograms were normal All patients with a normal electrocardiogram were under 1 month old

9 The electrocardiogram in 6 patients with single ventricle showed dominance of the left ventricular pattern All patients in whom the ÂQRS was in sextants I II and VI of Bayley s triaxial system had single ventricle

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Unusual QRS alterations seen in continuous Electrocardiocorder recordings

Instances associated with myocarditis, bundle branch block and angina pectoris

*John S. Gilson, M.D.**
Great Falls, Mont.
*Norman J. Holter, M.A., M.S., D.Sc.***
*Wilford R. Glasscock, B.S.***
Helena, Mont.

In our series of continuous electrocardiograms recorded on normal subjects by the Electrocardiocorder AVSEP† system, the QRS segment is an almost completely stable component of the PQRST complex during our customary 5 hour recording period regardless of body position, physical activity, or disease.[1] In our series of 400 consecutive recordings including both normal subjects and those with disease, only the 4 cases of this report developed gross transformations of the QRS segment during any single period of recording. Many cases (including these 4) did show minor variations, such as small changes in the over-all QRS amplitude or change in size of S waves during the recording period. In contrast to the relatively stable QRS segment, the more labile ST-T segment varied frequently and often to a striking degree, but such changes are not the subject of this report. These 4 examples of dynamic reversible QRS alterations illustrate what degree of change can be satisfactorily recorded and observed in the continuous electrocardiogram.

Methods

The Electrocardiocorder AVSEP system used to observe these cases and the concepts leading to their development are described in papers from the Holter Research Foundation Laboratory, Helena, Montana.[2] We used prototype instruments on loan from that laboratory for this study.‡ The Electrocardiocorder, a small device worn by the patient, produces a taped recording of electrocardiographic potentials. For these clinical trials we used a single bipolar lead, C_5R-C_5, which

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†AVSEP [illegible] registered trad[illegible] for A[illegible] permanent Elect[illegible] graph[illegible]

‡C[illegible] by Avion[illegible] Rese[illegible] Products Lo[illegible] A[illegible] C[illegible]

gives a pattern simulating V5.[4] AVSEP playback of the recorded tape is 60 times faster than recording speed so that each hour of recording is reviewed in 1 minute. The PQRST potentials are staggered as recorded simultaneously on both channels of the tape so that during AVSEP playback the sharp strong R wave potential from one channel triggers the oscilloscopic sweep which then traces the complete pattern recorded on the other channel. This arrangement produces patterns which begin an exact (but adjustable) fraction of a second prior to the R wave. It precisely superimposes successive R waves regardless of cycle length. When successive patterns are identical the superimposed patterns fit exactly. Gradual changes in pattern from beat to beat will produce a speeded up changing movielike effect in playback. Isolated aberrant patterns (such as ventricular ectopic beats) show a momentary flash of that pattern superimposed on the persisting previous trace. Changes in cycle length produce changes in length of the tail of the trace, a long tail corresponding to a slower rate. The photographs in this paper are from transparency snapshots of the AVSEP oscilloscope taken at an exposure of — of a second, a time which corresponds to 2 seconds of recording and usually includes 1 to 4 cardiac cycles.

Previous to the development of the

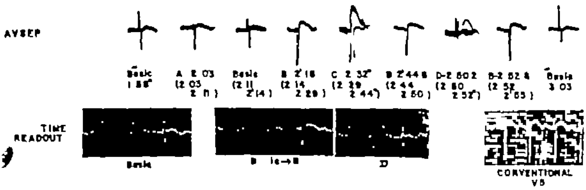


Fig. 1. Patient D. T., rheumatic myocarditis. *Upper row.* These are snapshots of the AVSEP oscilloscope screen made during playback of the Electrocardiocorder tape. The AVSEP basic pattern is that pattern predominant during the recording, usually associated with moderate heart rate and minimal physical activity. The variations from the basic pattern are so labeled with the time at which the snapshot was taken. The capital letters identify different patterns of variations. The times in parentheses indicate the period during which the pattern persisted. The initial pattern *Basic 1 58* in the upper row persisted unchanged throughout the first 2 hours and 3 minutes of Electrocardiocorder recording (2 minutes and 3 seconds of playback). The first variation *A 2 03* appeared suddenly and lasted 8 minutes (8 seconds of playback). This suddenly reverted to the third pattern which although it too is labeled basic differs slightly from the previous basic pattern. This second basic pattern in turn lasted 3 minutes of recording time. In the review of the next 41 minutes three other AVSEP variations suddenly appeared in sequence as illustrated. *A 2 03* represents a reversal of polarity without altered ST T segment. The several AVSEP variations labeled *B 2 18*, *B 2 44 B* and *B 2 52 B* all represent reversals of polarity with altered ST T segments as compared to that seen in the AVSEP basic. *C 2 32* looks very much like *A 2 03* but with superimposed ventricular ectopic beat. *D 2 50 2* seems similar to *C* but is not so clearly defined (see discussion of real time readout patterns below). At 3 55 of AVSEP playback time the basic pattern again appeared and persisted to the end of the 5 hour recording period. *Lower row.* These are segments taken from a real time readout made from the same Electrocardiocorder tape. The first section (labeled *Basic*) was produced from the first 2 hours and 3 minutes of Electrocardiocorder tape recording the period during which no QRS alternation occurred. This readout pattern corresponds to the AVSEP basic pattern above it and shows the relative fidelity of the pattern with the two methods of reproduction. The second section *Basic B* records that moment when the second basic pattern occurred (*Basic to B 2 18*). This confirms the sudden transition of essentially complete one beat and total transformation in the second. The third section *D* represents the pattern of ventricular ectopic beats alternating with a basic pattern (see upper row pattern *D 2 50 2*). What looks like preceding these ectopic beats are movement artifact. A conventional strip of V5 is also included for comparison with our basic (AVSEP). Pattern and the real time readout (Real time readout is our convenient term for conventional type Electrocardiographic record reproduced from Electrocardiocorder tape. This method is originated at the Holter Research Foundation Laboratory, Helena, Mont.)

Electrocardiocorder prolonged recording of electrocardiographic potentials has not been practical for subjects permitted unrestricted activity and free choice of locale. This new technique frees the subject from the restrictions of connecting wires or the limitations of radio transmission and reception. Without condensation of data as provided by AVSEP rapid review of extended records was also totally impractical.

The reasonably close approximation of the electrocardiographic patterns recorded with this system to those seen in other electrocardiographic records is a convenience but there is a distinct hazard in assuming that any given Electrocardiocorder AVSEP pattern has the same significance as a like pattern derived from conventional electrocardiographic methods. The signal in this new system not only comes from an unrestricted subject whose bodily position and activity can vary but that signal is processed through electronics which differ from conventional electrocardiographic recorders. Therefore the interpreter should be familiar with normal standards and typical patterns as seen with this technique including its characteristic artifacts.[1]

Clinical material

The entire series of 400 recordings in which these alterations of QRS were seen involved 273 subjects, 90 of whom were normal. They had from 1 to 3 recordings usually of 5 to 6 hours each. One hundred and eighty three were ill with a variety of diseases, some underwent operation during the recording period. All subjects were allowed any appropriate physical activity during the recording period (but muscle potentials produced during extreme physical effort occasionally obscure the AVSEP pattern temporarily). The 4 cases described below occurred in this group; the changes described are unique to these 4 cases.

We present these cases not as new electrocardiographic phenomena but as unusual changes in a relatively stable portion of the electrocardiographic complex and as changes observed under circumstances that are unusual in comparison to those which surround conventional recordings.

We had no clue from conventional electrocardiograms on these 4 subjects that these changes could be expected in the Electrocardiocorder patterns; other cases in the whole series with similar clinical or electrocardiographic diagnoses did not show these striking changes in the QRS segments under similar circumstances. As these cases illustrate, this method may give us a better appreciation of the full range of electrocardiographic responses both in normalcy and in disease by a system which permits prolonged recording in combination with condensed review of the data on subjects whose activity is not restricted by the requirements of the recording method.

Case reports

D. T. (Case No. 211), age 15, rheumatic myocarditis. This boy had had rheumatic fever in May 1961 with apparent recovery but became ill again in the fall. By Christmas he was in resistant cardiac failure and came under our observation shortly thereafter. He was severely dyspneic, showed a sustained fever, and had a diffusely enlarged heart, variable apical systolic murmur, and tic-tac heart sound (embryocardia). Antistreptolysin-O titer was 833 units; he was markedly anemic. At autopsy he showed a verrucous endocarditis and Aschoff nodules in a grossly dilated flabby heart.

He wore the Electrocardiocorder during a 5 hour period the day prior to his death. That morning the blood urea nitrogen was 32 mg per 100 cc, serum sodium was 133 mEq per liter and serum potassium was 4.5 mEq per liter. Although moribund, he moved occasionally in bed and, when responsive, complained of vague but severe discomfort. The patient took nothing by mouth during the recording period nor in the several hours preceding. He received a mixed intravenous solution of Lanoxin, Thiomerin, aminophylline and penicillin by slow steady drip prior to and during the entire recording period.

An unvarying pattern of QRS persisted during the first 2 hours and 3 minutes of the recording (2 minutes and 3 seconds of AVSEP playback). The alterations in QRS were sudden; they were complete over the period of 1 or 2 heartbeats (Fig. 1). The major alteration is the marked change in QRS polarity occurring both with and without associated change in the ST-T segment. The entire sequence during which these four alterations occurred lasted 52 minutes; the corresponding AVSEP review of the tape recording takes 52 seconds.

The changes in the QRS complexes as seen in this case have not been seen in records from any other individual observed either during the course of lying in bed or in the course of an active day outside the hospital, whether the subject was normal or ill. The changes seen in the AVSEP tracings did not coincide with shift in body position, with any particular discomfort, or with any circumstance

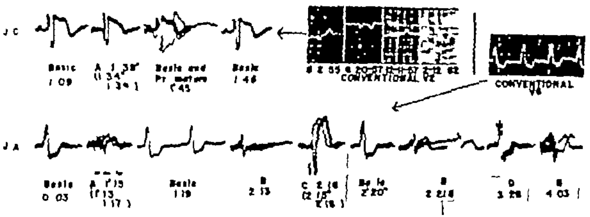


Fig (Fig 4 ...)

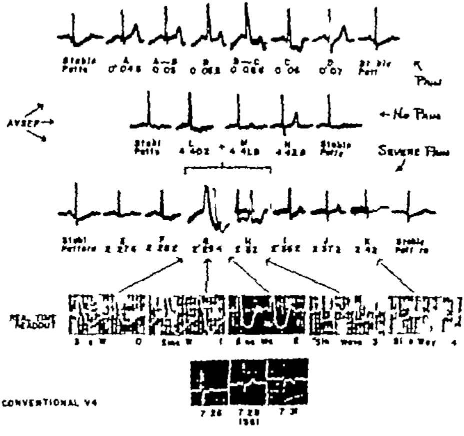


Fig 3 (Fig ...)

noted by the nurse technician who was in constant attendance throughout the recording period. P waves similar to those in the rest of the record are present preceding the bizarre complexes shown in the real-time readout strip in Fig. 3. They preceded all of the other changed complexes as well. The changes themselves were sudden and relatively brief and just as suddenly reverted to the original pattern.

J C (Case No. 01) age 59 right handed bank clerk. This man's bundle branch block appeared after a previous episode that was clinically consistent with a myocardial infarction. Since then he had suffered from angina until he had this second episode that was clinically consistent with another infarction (... elevated SGOT level). The examples shown in the upper sequence of Fig. 2 were recorded during the month after ...

The changes in the bundle branch block pattern occurred 15 minutes after the ingestion of ...

Fig 2 Patients J C and J A bundle branch block Conventions similar to those used in Fig 1 are used to identify the time of each AVSEP snap shot variations from the basic pattern are represented by capital letters followed by the playback time at which the picture was snapped *Upper series (J C)* The variation from the basic pattern is shown in *I 1 38* This variation appeared 15 minutes after ingestion of hot coffee and during a change in position The change involves a Q wave instead of an initial R and a slightly altered ST T segment After reversion to the basic pattern premature ventricular ectopic beats occurred as shown in the example *Basic and Premature 1 45* where the two types are superimposed We include this snap shot to emphasize our belief that the change shown in pattern *I 1 38* is not a ventricular ectopic beat further evidence is the presence of a P wave preceding the QRS The last snapshot in the sequence the resumed basic pattern *Lower series (J A)* The pattern labeled *Basic* resumed in the intervals between variations The shifts in patterns occurred suddenly The pattern *A 1 15* shows an M type QRS which obscured by a superimposed ventricular ectopic beat and some muscle potential The pattern was more obvious in the dynamic movielike AVSEP pattern than in this snapshot permanent patterns bine through the random pattern of occasional ectopic beats or artifacts *Basic 1 19* shows a return to the original pattern and also a failure of the sweep to retrigger so that two beats are seen in sequence rather than superimposed (a similar artifact occurs in *B 2 21 8*) The second snapshot *B 2 13* shows in addition to the variation a superimposed ventricular ectopic beat The third variation *C 2 16* and the fourth *D 3 28* also show in addition an artifact that we has termed offset which probably results from premature retriggering of the oscilloscopic sweep by a strong sharp muscle potential or strong alternating-current interference *D 3 28* shows only a notching of the R wave and more upright T wave to distinguish it from the basic pattern The last snapshot in the sequence *B 4 03* shows recurrence of the previous B pattern but combined with an offset artifact Conventional electrocardiograms on these two patients are shown in the upper right Those labeled *Conventional* I refer to Patient J C Our Electrocardiocorder record was obtained the day before *2 12 67* In this instance our recording reproduction system gives a pattern which differs greatly from that recorded by conventional means The other conventional strip is from Patient J A during the admission in which the AVSEP recording was made In contrast to those of J C this AVSEP pattern is virtually identical with the conventional tracing

Fig 3 Patient O A angina The upper three sequences were taken from a single 5 hour recording on a man with an eventual diagnosis of angina who died suddenly 3 months later Labeling convention are similar to those in Figs 1 and 2 AVSEP upper row This sequence was associated with mild anginal symptom spontaneously relieved The widening of QRS in *B 0 05 5* and *B C 0 05 8* should be compared to the initial and final patterns of QRS They should also be compared with the more extreme degree of QRS widening in the bottom AVSEP row example *G 2 29 4* Conventional appearing anginal S T and T wave changes are seen in *B B C* and *C* a taller more upright T wave than that seen in the stable pattern appears in the complexes preceding and following those showing QRS widening in the upper row The pattern in *B C 0 05 5* shows an electronic artifact with two different ST T patterns overlapped and criss crossed the elevated S T segment is actually associated with the flat T the more depressed S T with the upright T wave (obvious to the viewer watching the AVSEP screen but not so clear in the still snap shot) *AVSEP middle row* In this asymptomatic episode a lesser widening of QRS is shown in *L 4 40 2* and seen to be almost identical in appearance to that of *F 2 28 2* in the bottom sequence The extreme widening seen in the bottom row however does not occur but skip in *M 4 41 8* and *N 4 43 8* to patterns of QRS I similar to that in *J 2 37 2* in the bottom sequence This middle sequence is the more abortive of what might be termed the two incomplete sequences (top and middle) and was the only sequence without accompanying symptoms *AVSEP bottom row* This sequence coincided with severe pain when the patient awakened from an after lunch nap The most striking feature the extreme intraventricular block seen in *G 2 29 4* Some widening of QRS can be seen in both the preceding and the following snapshots *F 2 28 2* and *H 2 37* Shift in the S T segment suggestive of angina are also seen in those same examples Offset artifacts are seen in snapshots *G H* and *A* where electronic control of superimposition has been momentarily overridden by extraneous potential The dotted bracket and arrow show the bottom sequence pointing to the space between the *L* and *M* snapshot of the middle row indicate what we believe to be that part of the bottom sequence skipped in the abortive asymptomatic middle sequence If pattern *G* and *H* were to be inserted into the middle asymptomatic row the middle row would be complete and essentially the same as the bottom row *Real time readout* These cuts are segments of paper strips traced from the same magnetic tape recording out of which the bottom row AVSEP patterns were obtained The arrows point to the approximate area of the AVSEP sequence to which these cuts correspond The Sine Wave pattern *G 2 29 4* rapidly evolved changing almost imperceptibly from beat to beat it did not immediately transform as did the patterns in the cases of rheumatic myocarditis and bundle branch block previously described The widened QRS complexes shown in patterns *B* through *C* of the upper row and pattern *L* of the middle row likewise evolved with small increments from beat to beat On the rapid AVSEP playback the QRS complex of *B C* and *L* swiftly opened and closed The normal but short P R interval persists throughout the period of these changing patterns *Conventional* V These are conventional leads taken during this admission one was recorded on the day before and one on the day after our Electrocardiocord 5 hour recording which was made on 7 27 61 Although there are marked T wave changes they do not compare with the vivid changes shown in the AVSEP patterns (A sound produced by AVSEP by using the electrocardiographic potentials as a sound track and playing them through a speaker This produces a growl which changes somewhat with changes in pattern and/or rate During the playback of the intraventricular block shown in the lower of the three AVSEP sequences this growl deepened dramatically during the course of these changes in pattern in a manner not observed in any other cases in the entire series)

offec they ... anded with bi moving bout in bed when the linen was changed The ch nge la ted 5 minutes which orrespond to an AVSEP play back of 5 second He evidenced no symptoms nor were any changes observed by either the nurses or by the technician who monitored the recording This was the only change in pattern observed during the 5 hours of thi recording period

J 1 (Case No 176) age 83 left bundle branch block This woman also had a long standing bundle branch block and was hospitalized on this occasion with paroxy mal dy pnea and congestive cardiac failure The dy pnea and other signs of failure had been relieved for several days prior to this recording period However a persi tent and ery painful cystiti was under active treatment

The changes observed in her QRS complexes (Fig 2 lower sequence) were u ually associated with painful voidings The changes ere udden and complete over the period of a single beat they did not evolve rapidly as in the myocard tis (see above) or slowl as in the case of angina (see be low) On some occasions the changes occurred with no apparent change in activ ty but he was reticent to admit ny symptom to the technician who was in attendance during the recording period

COMMENT In both cases of bundle branch block I wa es can be identified preceding the complexes which show alteration and they how configura tion and P R interval imilar to those of the ba ic complexes I o othe ubjects w th bundle branch block in our entire group no other imilar alter ons in QRS configuration were noted

J O A (Case No 145) age 68 atypical angina This man was hospitalized for evaluation of post prandial epiga tric pa n Previou recent medical care elsewhere ... f diet and anti pasmodic antacid therapy w un ucces f l even though he reported occa ional rel ef of mptoms by further eating On closer questi ning he revealed the fact that he experienced pain the right arm but onl if the epiga tric pain w re severe Se en years previousl a su p cion f ngina had been di carded after the exercise electrocardiogram wa found to be normal and aft r an x ray impression of duodeniti had been followed by a favorabl response to regimen for ulcers During thi ad m ion and ubse quent to thi record he improved clinicall on a program of reduction in diet nitro glycerin ... anticoagulants and modi fication of work He d ed uddenly a few months after th tracing had been obtained no autopsy was obtained

The three AVSEP sequences pictured in Fig 3 all occurred during a ingle 5 h ur period tape recorded by the Electrocardiocorder The lower sequences la ted nly a fraction of a second on the AVSEP playback (a fr ct on of a m nute in real time) but in the most extreme exampl it la te l for well over a secon l of playback time In all these sequences the P w ves and n unchanged P R interval continue t precede the changing com plexes

He ment oned pain twice during the recording session Both instances coin ided with widened QRS complexes The other widening occurred without symptoms We infer therefore from the electrocardiographic similarities of the asympto matic epi ode to the more symptomatic sequence that imilar electrophysiologic changes occurred in each instance but were associated with pain only when the changes were more marked

In our first review of thi tape we were startled by the rapidly widening QRS complex as shown *in the bottom sequence in Fig 3 G 2 29 4* This appears to be rapid waxing and waning of a severe intraventricular block The very gradual change from beat to beat is hardly noticeable in successive complexes recorded conventionally in the real time readout (Fig 3) in the same way that adjacent frames in ordinary movies how barely perceptible changes The pattern appears on the AVSEP screen as though the two limbs of the R wave were rapidly opened and closed like the two blades of a pair of scissors On re review of the tape we noted the lesser degrees of intraventricular block in the other two sequences The magnitude of the change is beyond that usually seen in conventional electro cardiography during angina It also exceed any thing seen in other recordings in our series of 400 whether the subject were suffering from angina or from some other disease or whether they were entirely well On the other hand the associated S T segment and T wa e changes in the e sequences are characteri tic of nginal type lectrocardio graphic pattern whether reproduced by this new method or con entional exercise electrocardio grams

Discussion

The alterations hown are the only marked changes in QRS configuration observed during our use of this new Elec trocardiocorder AVSEP system in 400 trials Although we almost always see some variation in the depth of the S wave and often see a change in the ratio of R to-S amplitudes we believe that such minimal variations reflect only small and probably insignificant vector shifts These 4 cases stand out because they show both uncommon and extreme variations from the subject s basic pattern In our ex perience in recording with this system in both normal and ill subjects the QRS portion of the entire PQRST complex is the most stable of the various components of the electrocardiographic pattern [1]

These examples are not presented with any attempt to characterize their clinical importance or to imply any new knowledge of the electrophysiology of the heart but to emphasize the magnitude of reversible changes in the electrocardiogram which can occur during the course of prolonged observation under unrestricted circum

Included ... to reach the ... of F J ... M D ... Cl ... Ge ... Mont

stances They also show how quickly and how much the spread of potentials through the myocardium can change without any obvious change in the subject's clinical status

The persistence of P waves and of unchanged P R intervals preceding all the alterations combine to minimize the possibility that these changes are due to ectopic beats Furthermore we believe that the alterations illustrated are not technical artifacts Not only are P waves present but the contours of the altered complexes are too regular in pattern and frequency to be extracardiac in origin Artifacts as seen in these snapshots are relatively rare considering the degree of subject activity Artifacts do not obscure the patterns as much when they are viewed on the oscilloscope as in the snapshots because artifacts are usually less persistent than the dominant pattern

Conventional electrocardiograms or even the more recent electrocardiographic monitor techniques would seldom catch transient changes such as those seen in the *fourth* case (O A) *We have observed* such transient widening of QRS in only this one record out of over 50 5 hour recordings on patients with angina The slight changes occurring during such a short time as in this patient's two lesser examples especially might not be included in the brief samplings taken by intermittent recording methods or even if recorded might be overlooked by the interpreter of the record because of their brevity and slight magnitude The most marked change pictured from this case is too gross to miss if it were caught with any other current method but the progressive nature of its accretion and regression might be overlooked Similarly the alterations in the two cases of bundle branch block are unusual enough that none were observed in 7 other subjects with bundle branch block who had similar 5 hour recordings The infrequency and unpredictability of these changes or of any other similar changes would make them difficult to discover by any technique which did not condense the review of prolonged records Even with monitor electrocardiograms whether taken by radio or oscilloscopic projection or both the lack of data reduction in such systems might allow changes to pass unnoticed even if observer fatigue were somehow overcome

We postulate that the changes in the case of rheumatic myocarditis may represent some electrochemical alteration in the myocardium related to the inflammation which caused a change in the depolarization pattern alone in the first variation shown in Fig 1 *A 2 03* and in both depolarization and repolarization in subsequent AVSEP variations The changes may be due to factors other than the disease but we believe that they are not technical artifacts nor are they due to a change in position by the subject A nurse technician who remains near the subject records the time of any symptom incident or activity so that we can accurately correlate any changes in pattern with the clinical circumstances at that moment If they were a consequence of change in body position we would have expected them to coincide with his movements and to have occurred repeatedly throughout the record On the other hand we do be*lieve that the variations in the QRS* pattern in the subjects with bundle branch block did result from activity The pathway taken by the wave of excitation through unspecialized cardiac muscle when the specialized conduction tissue is blocked might be expected to vary with activity meals position internal pressure or changes in temperature etc The changes that we observed coincided exactly with activity along with such environmental changes

As illustrated in the fourth case the association of delayed or detoured conduction to the subject's anginal attacks seems to be clear The changed QRS duration not only coincided with anginal pain but also coincided with characteristic anginal changes in the associated ST T segments We have observed that anginal ST T segment changes as seen by this method are comparable to those recorded by conventional means[4] Further relationship of this intraventricular block to his angina is suggested by noting that the magnitude of the block in the two symptomatic episodes was roughly proportional to the intensity and duration of the pain The asymptomatic abortive episode

(shown and described in Fig. 3) had the least and briefest widening; anginal ST-T segment changes were less marked than but were similar to their symptomatic counterparts.

That this transient progressive widening must be a rare phenomenon is shown by our failure to observe it in any of our other 400 records, including those from 51 patients with angina, regardless of the subject's clinical status. We have *not* been aware previously of *gradually* waxing and waning intraventricular block as a clinical entity at all and consequently *not* as a concomitant of angina. Such block could represent an altered course of depolarization and repolarization as a temporary consequence of poorly functioning or nonfunctioning ischemic myocardium.

Whether changes occur rapidly over the period of a few beats, as in our case of rheumatic myocarditis, or relatively slowly, as in the instance of gradual development and regression of extreme intraventricular block during dozens of successive beats, the Electrocardiocorder AVSEP method reproduces the change vividly. The method not only provides a more convenient technique for discovering transient and/or infrequent electrocardiographic phenomena but also provides an accentuated display of the change so that the unusual pattern will be readily noticed by the observer.

Summary

Only 4 cases were found to show both striking and reversible alterations in the QRS portion of the electrocardiographic complex in our review of over 400 5-hour (or more) recordings from a miscellaneous group of 273 subjects using the Holter Electrocardiocorder AVSEP system to record continuous electrocardiograms. Snapshots of the basic pattern in each case are contrasted with the variations from that pattern to show the alteration in QRS.

A case of myocarditis was associated with sudden reversals of polarity both with and without changes in the ST-T segment. Two cases of bundle branch block showed changes in the pattern of the QRS associated with change of position and voiding. The fourth case showed three episodes of intraventricular block which coincided with expressions of anginal pain, the pain being proportional to the amount of block.

These 4 instances of striking and reversible changes in the usually stable QRS portion of the whole electrocardiographic complex emphasize the unique utility of this system in capturing relatively *infrequent* variations in the continuous electrocardiogram. They suggest the potential value of this continuous electrocardiographic monitor system which is free of the previously necessary restrictions upon subject activity and/or subject locale. This system makes possible a new scope of electrocardiographic observations and permits the development of some concept of how great a variation may occur in the electrocardiogram during the course of daily activity or during illness.

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Experimental and laboratory reports

Further studies of the electrocardiographic effects of experimental myocardial lesions

*J. A. Abildskov, M.D.**
Robert S. Boyle, M.D.
Salt Lake City, Utah

Further definition of the mechanisms by which localized myocardial lesions alter the electrocardiogram is necessary to achieve the full utility of electrocardiographic records in the diagnosis of myocardial infarction. Information concerning the sequence of ventricular activation which is now available can be utilized in such investigations of the mechanisms of alteration of the QRS complex. Theoretical, experimental, and clinical studies in which the excitation sequence reported by Scher was so employed have been reported previously.[1-4]

In the previous experimental study, lesions were produced by the injection of a necrosing solution into the ventricular wall of dogs through the unopened chest. This procedure avoided the complex electrocardiographic effects of thoracotomy; however, little control of the location of the lesions was possible. In particular, lesions restricted to subepicardial and posterior basal portions of the left ventricle were not obtained in that study, and only one lesion restricted to the right ventricular wall was produced.

In the present study, an open-chest preparation was employed together with measures designed to minimize the electrocardiographic effects of thoracotomy. With this preparation, the placement of lesions could be controlled more exactly than was possible in the previous experiments, and subepicardial, posterior basal, and right ventricular lesions were obtained.

Materials and methods

Experiments were performed on 12 dogs which ranged in weight from 10 to 26 kilograms and which were anesthetized with pentobarbital. A total of 25 localized myocardial lesions was produced. Tracheotomy was performed and artificial respiration carried out using a respirator which could be halted at a fixed phase of the respiratory cycle. All electrocardiograms were recorded within a few seconds after respiration was halted.

The chest was opened with a mid-sternal incision extending from the xiphoid to a level near the base of the ventricles, and the chest wall was retracted only enough to permit placement of a needle at the desired site in the heart wall. This needle, through which a necrosing solution was to be injected, was inserted through the intact pericardium. Needles of 20 gauge

From the Department of Internal Medicine, University of Utah College of Medicine, Salt Lake City, Utah.
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*Address: Department of Medicine, State University of New York Upstate Medical Center, 766 Irving Ave., Syracuse, N. Y. 13210.

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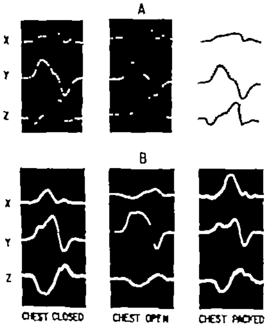


Fig. 1. *A*. QRS complexes of electrocardiograms recorded 1 hour apart in dog in which the opened chest was packed with saline-soaked shredded polyurethane. Superimposed tracings of these complexes are shown at the right of the figure and illustrate the reproducibility of QRS form under the conditions of the experiments reported. *B*. QRS complexes recorded before and after the chest was opened and after packing of the open chest with saline-soaked shredded polyurethane.

sidered to be a point on the mid sternal line two intercostal spaces above the maximum cardiac impulse determined by palpation. The electrodes of the orthogonal leads system were placed in appropriate relation to this point with the chest closed and were replaced to approximate the same relation to the heart after the chest had been opened.

As could be anticipated, the form of the prethoracotomy and post thoracotomy records and those obtained after packing the chest cavity always differed. There was a consistent difference in the anteroposterior component of the QRS in prethoracotomy and post thoracotomy records with deflections in the Z lead always being small in the post thoracotomy records. Packing the chest cavity in the manner described had the consistent effect of increasing the amplitude of deflections in this lead. Examples of prethoracotomy and post thoracotomy records and those obtained after packing the chest cavity are shown in Fig. 1 *B*.

Time phase of control and post lesion records. Since many of the lesions produced in this study altered only part of the QRS complex, the means by which the time phase of pre lesion and post lesion records was identified requires comment.

Records associated with 17 of the lesions showed alterations of only the mid temporal and terminal portions of the QRS complex. At least the initial one third of the QRS in all three orthogonal leads of pre lesion and post lesion records could be superimposed. In one experiment alterations of the QRS were confined to the initial one third of the complex and mid temporal and terminal portions of pre lesion and post lesion complexes could be superimposed. These findings provided reasonably certain identification of the proper time phase of those records.

Identification of the absolute time phase of the records associated with the other 8 lesions was not so certain. In these cases the QRS form in at least two of the orthogonal leads of pre lesion and post lesion records could not be matched in any time phase relation. Thus, although the absolute time phase of these records could not be determined, it was certain that initial as well as later portions of the QRS complex had been altered.

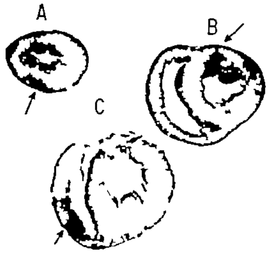


Fig. 2. Cardiac sections showing portions of three lesions produced in this study.

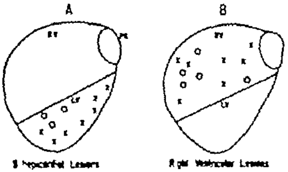


Fig. 3. Approximate location of lesions produced in this study. Lesions at the sites indicated by circles altered initial as well as later portions of the QRS complex whereas those at the other sites indicated altered only mid-temporal and terminal portions of the QRS.

Characteristics of the lesions. Although standard amounts of formalin solution were injected, the size and shape of the resulting lesions varied. The irregular shape of the lesions makes it difficult to specify their size, but their location within certain areas was noted. These locations will be described *together with the electrocardiographic effects of the lesions.* Examples of the lesions produced are shown in Fig. 2.

Electrocardiographic effects of subepicardial lesions in the left ventricle. Eleven lesions restricted to the subepicardial one half of the left ventricular wall were produced. The approximate location of these lesions is indicated in the diagram in Fig. 3A. Three of the lesions which were located near the interventricular septum and which are indicated by circles in the diagram altered *initial* as well as mid-temporal and terminal portions of the QRS complex. The other 8 subepicardial lesions of the left ventricle altered only mid-temporal and terminal portions of the QRS.

The direction of QRS alterations with relation to the location of individual lesions was variable. This was consistent with the expected effects of loss of subepicardial tissue and with available *information concerning* the ventricular excitation sequence. With all localized myocardial lesions, the form of the QRS complex is determined by the activation pattern in uninvolved portions of the ventricles. In the case of subendocardial and intramural lesions, the widespread extent of the excitation process at the time the area of the lesion would normally have been activated often leads to marked displacement of the heart vector away from the location of the lesion. The magnitude of the heart vector may be either increased or decreased by the presence of the lesion.[3] With subepicardial lesions, the activation process existing at the moment the area of the lesion would normally have been excited is less extensive. This leads to a less marked displacement of the heart vector *than is often* the case with lesions in other locations. A more regular effect of decreasing the magnitude of the heart vector is also to be expected with subepicardial lesions. The effect of a decrease in magnitude of the heart vector may exceed that of displacement of the vector with respect to an individual lead axis. As an example of such an effect, it is possible that an anterior wall subepicardial lesion may actually result in a decreased posterior component of ventricular activation. These considerations seem to be adequate *to account for* the variability in the direction of alteration of the QRS which occurred with subepicardial lesions.

The changes in the QRS complex which resulted from subepicardial lesions were small relative to those which often occurred with similar lesions in intramural and subendocardial areas in a previous study.[3] The relatively small QRS alterations in the present study were consistent with simple loss of tissue as the mechanism of the alterations. The theoretical effects of subepicardial lesions derived from the excitation sequence reported by Scher were also small. These results are illustrated in Fig. 4. In *A* of that figure the effects of a subepicardial lesion in the apical portion of the anterolateral left ventricular wall are shown. The oscilloscopic traces shown are the control and post-lesion XYZ leads. Superimposed tracings of the QRS portions of these records are shown at the right of the figure with the control form indicated by solid and the post-lesion form by dotted line. The QRS alterations associated with this lesion were confined to mid-temporal and terminal portions of the QRS complex and include alteration of the slope of the de-

scending limb of the R wave in leads X and Y.

Fig. 4 B shows the effects of one of the 3 subepicardial lesions located near the interventricular septum which altered initial as well as terminal portions of the QRS complex. All three orthogonal leads were altered by this lesion, with the most marked effect being a decreased amplitude of both Q and R deflections in the Z lead.

The theoretical effects of a lesion of the subepicardial anterior wall are illustrated in Fig. 4 C. Leads X and Z shown were derived from the excitation sequence reported by Scher. The control form of these derived leads is shown by a solid line and the form of the leads derived after a postulated lesion at the site illustrated are shown by the dotted lines. The effects of the lesion were confined to mid temporal and terminal portions of the QRS and consist of slight alterations in the peak amplitude and slope of the R waves.

BASAL LEFT VENTRICULAR LESIONS. Two transmural lesions were produced in the posterior wall of the left ventricle near its base. Despite their transmural extent these lesions altered only mid temporal and terminal portions of the QRS complex. Both lesions decreased the amplitude of the R wave in lead Z, reflecting a decreased posterior component of ventricular excitation, and decreased the amplitude of an S wave in lead Y, reflecting a decreased superior component of activation. Both of these effects are consistent with simple loss of tissue in the posterior and basal portions of the heart.

RIGHT VENTRICULAR LESIONS. Right ventricular lesions were produced at the approximate sites indicated in the diagram in Fig. 3 B. Ten of these lesions were transmural and 2 were restricted to the subepicardial one half of the ventricular thickness. Lesions at the sites indicated by circles in the diagram altered initial portions of the QRS complex and all but one of these also altered mid temporal and terminal portions of the complex. Lesions at the other sites indicated altered only mid temporal and terminal portions of the QRS complex. As is evident from the diagram 4 of the lesions which altered early portions of the QRS complex were located in the right lateral wall of the ventricle and one was located near the interventricular septum. These findings are consistent with Scher's excitation sequence data which indicates early activation of the right ventricular wall in both of these areas. The magnitude of QRS alterations due to right ventricular lesions was small and qualitatively consistent with the expected effects of right ventricular lesions as shown in Fig. 5.

In Fig. 5 A the effects of a lesion in the

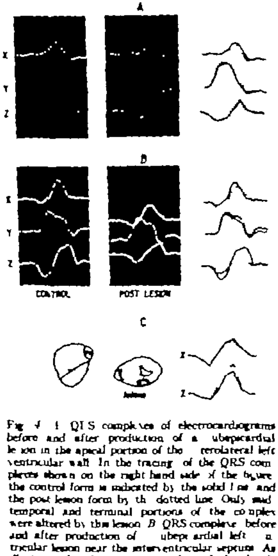


Fig. 4. A, QRS complexes of electrocardiograms before and after production of a subepicardial lesion in the apical portion of the anterolateral left ventricular wall. In the tracings of the QRS complexes shown on the right hand side of the figure the control form is indicated by the solid line and the post lesion form by the dotted line. Only mid temporal and terminal portions of the complex were altered by this lesion. B, QRS complexes before and after production of a subepicardial left ventricular lesion near the interventricular septum. As illustrated by the tracings on the right hand side of the figure initial as well as later portions of the complex were altered by this lesion. C, QRS complexes in X and Z leads derived from the excitation sequence reported by Scher are shown as solid lines. The theoretical effects of the subep... illustrated are shown by the...

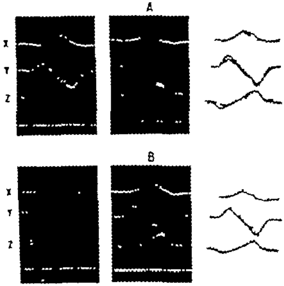


Fig. 5. A, QRS complexes from an experiment in which a lesion in the right lateral portion of the right ventricular wall was produced. As shown by the superimposed tracings of these complexes, initial as well as later portions of the complex were altered by this lesion. B, QRS complexes from an experiment in which a lesion in the anterior portion of the right ventricle was produced. Only mid-temporal and terminal portions of the complex altered.

right lateral portion of the right ventricular wall which altered both initial and terminal portions of the QRS are shown. The effects of a lesion in the frank anterior wall of the right ventricle which altered only mid-temporal and terminal portions of the QRS complex are shown in Fig. 5 B.

Discussion

The result with most significance to the electrocardiographic diagnosis of myocardial infarction was the finding that many lesions confined to the subepicardial half of the left ventricular wall and even transmural lesions in the posterior basal wall altered only mid-temporal and terminal portions of the QRS complex. Such alterations would not be recognized as the result of localized lesions by standards which require abnormalities of the initial portion of the QRS, such as pathologic Q waves. The finding that most subepicardial lesions did not alter initial portions of the QRS complex is not consistent with reported evidence that activation of only subepicardial portions of the ventricles contributes to the form of QRS complexes.[2] Another finding which is relevant to diagnostic use of the electrocardiogram in the recognition of localized lesions was the small magnitude and the variable direction of alterations produced by subepicardial lesions. It seems likely that most lesions in this location would not be recognized by current electrocardiographic standards and techniques.

Another finding of interest was that the electrocardiographic effects of subepicardial lesions near the interventricular septum differed from those of similar lesions elsewhere in the left ventricle. Lesions near the septum altered initial as well as later portions of the QRS complex. Such alterations which extended over the entire duration of the QRS complex may have been the result of a conduction disorder of the peri-infarction block type as well as of simple loss of tissue. These findings are compatible with, although they do not prove, intramural extension of the specialized conduction system near the interventricular septum. Some lesions in the right lateral wall of the right ventricle and in the right ventricle near the interventricular septum also altered early as well as late portions of the QRS complex.

There are a number of features of the present study which limit its significance. As in previous studies of localized myocardial lesions, it is impossible to exclude factors other than the lesions themselves which may have contributed to electrocardiographic alterations. The necessity of conducting these experiments with the chest open definitely limits the significance of the results even though normal volume conductor properties of the thorax were partially restored by the procedure of packing the chest cavity. The variability of the size and shape of the lesions also limits the conclusions which can be drawn from the findings, and the variability of the form of the control records constitutes a similar limitation.

Despite the shortcomings of the study, the results appear to be a further step in the definition of the electrocardiographic effects of localized lesions and their mechanism.

Summary

The electrocardiographic effects of 25 chemically produced myocardial lesions in dogs were studied Eleven of these were restricted to the subepicardial half of the left ventricular wall 2 were located in the posterior basal portion of the left ventricle and 12 were located in the right ventricular wall

Eight of the 11 subepicardial left ventricular lesions altered only mid temporal and terminal portions of the QRS complex The other 3 lesions were all located near the interventricular septum and altered early as well as later portions of the QRS

The 2 lesions of the posterior basal left ventricular wall altered only mid temporal and terminal portions of the QRS complex

Right ventricular lesions in the right lateral wall near the base and those near the interventricular septum altered early as well as late portions of the QRS complex Other right ventricular lesions altered only mid temporal and terminal portions of the QRS

The significance of these findings may be summarized as follows (1) Lesions in a variety of locations cannot be recognized by electrocardiographic standards which require abnormalities of the initial portion of the QRS complex (2) Recognition of the relatively small and variable electrocardiographic effects of subepicardial posterior basal and right ventricular lesions may require modification of current clinical electrocardiographic techniques and standards for the diagnosis of myocardial infarction (3) The finding that most subepicardial lesions did not alter initial portions of the QRS is not consistent with reported evidence that activation of only subepicardial portions of the heart contributes to the form of QRS deflections

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An experimental study of the electromotive forces of the heart

Ernest W. Reynolds, Jr., M.D.
Daniel A. Weller, M.D.
Ann Arbor, Mich.

Progress in understanding the relationship between differences in potential measured in a lead and the electromotive forces of the heart has been closely related to the improved understanding of the nature of these forces and the development of the concepts of the lead vector[1] and lead field. The latter concepts permit us to explain how the electromotive forces of the heart produce voltage in leads in finite and nonhomogeneous media. With regard to the electromotive forces themselves, the studies of Craib and Canfield[2] and Wilson replaced the crude dipole model proposed by Waller[3] in 1889 with a more sophisticated picture of the heart's electrical activity as generated by a complex of electromotive surfaces located at the junction between active and resting muscle. At any instant of time this junction constitutes a continuous layer within the confines of the heart, with its positive side toward resting tissue and its negative side toward active tissue. A single element of this surface produces an electrical field equivalent to that produced by a dipole consisting of a point source and point sink of current of equal size and close to one another.

The potential equation for an electromotive surface consisting of two layers placed in a resistive, linear, and isotropic media of infinite size is

$$V = \pm \frac{1}{4\pi} \int_s E \, d\omega + C$$

where V is the potential at a point in the media, E is the difference in potential across a single element of the electromotive surface, and $d\omega$ is the solid angle subtending a single element of the electromotive surface. The constant, C, used when evaluating *a single potential, disappears* when evaluating the difference in potential between two points in the media. *If E is constant for every element of electromotive surface*, then integration yields

$$V = \pm \frac{E}{4\pi} \Omega + C$$

where Ω is the solid angle subtending the *boundary of the entire electromotive surface*. The fact that the surrounding medium is nonhomogeneous and finite does not *substantially detract from the usefulness* of this equation, since it is usually approximately true even for finite nonhomogeneous *conducting media*.

In the special case of a closed electromotive surface of any shape, the difference in potential between any point inside the closed surface and any outside point is

[illegible]

simply equal to the difference in potential F across the electromotive surface. The difference in potential between any two points outside a closed electromotive surface is zero provided that the difference in potential across the electromotive surface is uniform. In the special case under consideration these conclusions are applicable even in a nonhomogeneous conducting media.

The relations developed for an electromotive surface apply at a single instant of time for a propagated wave; thus the situation must be analyzed from instant to instant treating each position of the wave as static. The dimensions of a real wavefront are finite. Durrer's[4] measurements indicate that the wavefront in the outer three fifths of the myocardial wall is sharply bounded and regular in form. The distance between the sources and sinks of the activation wave in these layers is ordinarily less than 1 mm.

The present study is an attempt to measure the external field associated with propagated activity which should in theory produce a closed electromotive surface. The value of this type of experiment is that it provides evidence that a propagated wavefront has a uniform difference in potential across its surface.

Methods

Ten dogs were anesthetized with pentobarbital 50 mg per kilogram, intubated and maintained with an alternator type of respirator. The chest was opened long enough to permit implanting the stimulating and recording electrodes. Since one requirement of the study was to permit simultaneous stimulation and recording from the same intramural site, ordinary electrical methods of stimulation which tend to block the recording amplifiers cannot be used. To remedy this mechanical stimulation was used since this method produces less stimulation artifact. Early in this study a simple wire probe placed inside a hypodermic needle which was insulated except at the tip was used to mechanically stimulate the heart at a known depth.[7] The wire probe was simply tapped by hand until by chance the mechanical stimulus so produced fell after the refractory period and produced a propagated beat. To obviate the difficulties caused by the refractory period of the heart a method of synchronizing the mechanical stimulus to the cardiac electrical cycle was developed. This was accomplished by driving the atria at a constant rate with an electronic stimulator. A second stimulator synchronized to the first by a variable delay drove a relay which in turn actuated a solenoid to deliver the mechanical stimulus. The solenoid shown in Fig. 1 contained 25 turns of No. 22 copper wire wound around an iron core. On the application of a 20 msec 6 volt D.C. pulse from the relay the self contained stylus plunger descended sharply 1 mm beyond the tip of the hypodermic needle affixed to the base of the solenoid. In actual use the needle was inserted to a depth of from 2.5 to 6 mm into the myocardium and the solenoid was sewn to the surface of the heart. This arrangement permitted the automatic delivery of the mechanical stimulus at any time in the cardiac cycle desired. The base of the solenoid and the tip of the needle acted as recording electrodes. In addition other plunge elec-



Fig. 1. The solenoid stimulator for producing mechanically stimulated intramural ectopic beat (closed electromotive surface). The plunger that produces mechanical stimulation is contained within the hypodermic needle. The tip of the needle serves as central (intramural) recording electrode and the round silvered disk mounted flush with the plastic base is the surface recording electrode.

trodes were placed near the endocardial surface and at various depths within the myocardium lateral to but within a radius of approximately 10 mm from the tip of the stimulator. After the electrodes had been sewn in place the dog's chest cage was closed.

To record accurately the small time differences involved the electrograms were recorded on a Hathaway oscillograph having a paper speed of 1,130 or 620 mm. per second. The mirror type of coil galvanometers used were driven by Tektronix Type 122 S1 preamplifiers so that the over-all frequency response was 0.04 to 210 c.p.s. The voltage was reduced 36 per cent at the latter frequency.

Twenty-four experiments were carried out in 3 dogs using the hand-operated wire probe stimulator and 60 experiments were carried out in 7 dogs using the solenoid. The results were similar with both methods of mechanical stimulation although fewer artifacts were seen with the hand-operated stimulator. Synchronous recordings were made from the tip of the needle, called the central lead, and one or more of the electrodes placed around the central lead point, usually the adjacent ventricular surface and occasionally from one of the electrodes located on the endocardium or at the same depth in the myocardium but lateral to the central lead point. No special advantage is attributed to one of these recording sites and the surface electrode was the simplest to use since the distance between the central tip and the surface electrodes was fixed and could be measured accurately. The right leg was used as the reference voltage.

Results

The central lead showed an initial negative deflection in all 24 of the hand-operated mechanical stimulator experiments and in 58 of 60 solenoid experiments. In the latter unpredictable artifacts were produced in the central lead and in 26 of these a small initial positive deflection preceded the main negative deflection. Since the intervals between the onset of electrical activity in the central lead and nearby surface or intramural sites were similar in both sets of measurements and the isoelectric interval in the surface lead was not disfigured by these artifacts, the results obtained using the solenoid technique were retained. Electrical activity was measured by any displacement of the base line as recorded at the central electrode.

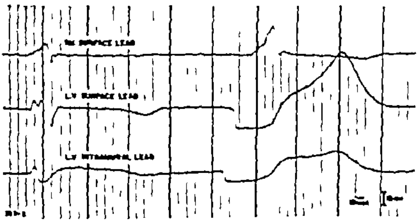


Fig. The normally propagated beat seen at the left shows synchronous onset of electrical activity but in the intramural ectopic beat at the right there is a 17.1 msec. period in which the left ventricular surface lead is [illegible] with respect to the intramural lead located in the the middle layer. Th[illegible] tr[illegible] surface penetrated th[illegible] and [illegible] surface first in th[illegible] distance [illegible] the left ventricular surface [illegible] The upper trace [illegible] of electrocardiographic surfaces and [illegible] that [illegible] over the right ventricle [illegible] the [illegible] the left ventricle [illegible] distance [illegible] and the small size of the electrode [illegible] surface at th[illegible] time.

preceded that at the adjacent surface recording by a mean value of 10 6 msec in the hand-operated stimulator experiments where the stimulator tip was placed at a depth of 5 mm in the myocardium Thus the mean conduction velocity for the 5 mm distance separating the two recording electrodes was 470 mm per second in this group of experiments Fig 2 is an example of the propagated wave reaching the epicardial surface first as indicated by a negative deflection in the left ventricular surface lead The period between the onset of electrical activity at the central lead and the onset of electrical activity at the left ventricular surface lead is 12 1 msec and during this interval the difference in potential produced in the left ventricular surface lead is negligible Recordings made from these electrodes during the production of extrasystolic beats at many other sites or during normal activity showed electrical activity which was considered to be synchronous i e the onset of the deflection in the several leads was within 1 or 2 msec as compared with the 5 to 23 msec for the intramural beat described An example of a normally propagated beat is shown on the left hand side of Fig 2

In one instance illustrated in Fig 3 propagation reached the endocardial surface first as shown by the positive deflection in the left ventricular surface lead The isoelectric interval between the onset of electrical activity at the central electrode and the left ventricular surface lead was 23 2 msec This interval is almost twice as long as that observed in the other experiments and suggests that propagation to the endocardium pursued a tangential course In this example as in all of the others the external field produced by the propagated wave is negligible until the wave reaches the ventricular surface Table I gives a summary of all of the measurements made over the anterior and posterior walls of the left ventricle and the anterior wall of the right ventricle The column on the right which gives the calculated depth of stimulation serves as a check on the positioning of the electrode tip The measurement I to S is the duration of the isoelectric interval The variations in voltage during this interval were of the same order of magnitude as shown in Figs 2 and 3 The sensitivity of the recordings was 10 mv = 1 cm which is considered to be adequate for direct leads

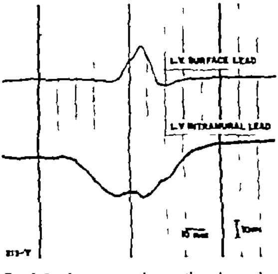


Fig 3 Synchronous recording with exploring electrodes located 5 mm apart and using the right leg as a common reference The intramural electrode located at the point of origin of the propagated beat record an initial negative voltage, whereas the surface lead remains isoelectric for 23 2 msec Activation must have penetrated the endocardial surface first since the surface lead is positive and the solid angle subtended at the surface point by an open electromotive surface would then face the positive side of the open electromotive surface

Discussion

It is assumed in this study that propagated wavefronts which do not present to either the epicardial or endocardial surfaces are temporarily closed electromotive surfaces Since the external field produced by these closed electromotive surfaces is negligible even when measured by external electrodes placed a few millimeters distance from the wavefront this strongly suggests that the difference in potential across these closed electromotive surfaces is uniform or otherwise such self-cancellation would not occur Certainly the small variations in potential observed during the isoelectric interval as depicted in Figs 2 and 3 would not be measurable at the body surface

It is reasonable to assume that propagated wavefronts have similar characteristics whether they are closed or whether they have boundaries on the epicardial or endocardial surfaces of the heart There

Table I. Summary of measurements of the duration of the isoelectric period from the onset of electrical activity at the central stimulating electrode (I) to the superjacent surface electrode (S)

Depth of electrode tip (mm.)	Number of measurements	Mean duration I to S (msec.)	Calculated depth of stimulation (mm.)
Anterior wall of left ventricle			
4	23 Solenoid	8.5	4.2
5	24 Hand stimulated	10.6	5.3
Posterior wall of left ventricle			
2.5	27 Solenoid	7.4	3.0
6	6 Solenoid	8.3	4.1
Anterior wall of right ventricle			
2.5	16 Solenoid	7.5	3.7
5	7 Solenoid	8.4	4.2

[illegible] propagation in the outer layer of 300 mm. sec. [illegible] calculated depth

fore, the present studies would also suggest that a uniform difference in potential exists across all propagated wavefronts in normal ventricular muscle.

Although the absolute value of E, the difference in potential across the electromotive surface, could not be measured accurately in the present study, it is obvious from inspection of Fig. 3 that E has a value of the order of one sixth to one fourth of the transmembrane resting potential to which it is related. This reduction in voltage is believed to be related to the physical separation of cardiac fibers by interstitial spaces containing capillaries and producing holes in the electromotive surface, as well as the shunting effects of interstitial fluids and by other factors as discussed by Scher. If these holes were uniformly distributed, the closed electromotive surface would still be self-cancelling, but would show a reduced voltage across its surface.

Some consideration should be given to the possibility that the data as derived from this study are subject to other interpretations. The mass of tissue involved in the spread of activation which follows intramural stimulation may be too small to give a recognizable deflection in the adjacent ventricular surface lead, whether the electromotive surface is uniform or not. The other possibility is that the observed voltage cancellation which occurs in surface leads is the result of a peculiar distribution of electromotive forces across the electromotive surface which may cause cancellation but which is far from uniform. One may visualize a quadripolar distribution of electromotive forces where the external field would not be zero but would be very small.

It is thought that these objections are not serious, since the variations in potential observed in leads located as close as 2.5 mm. to the centrally stimulated point were no greater than those observed in more distant leads. The possibility of cancellation occurring as a result of an unusual distribution of electromotive force on the electromotive surface is thought to be small, since the large number of measurements of the right, left, lateral, and diaphragmatic portions of the heart should exclude this from occurring by chance. In addition, other measurements using differential electrodes point to the fact that the spread of activation during these experiments was not concentric or symmetrical but generally followed the direction of cardiac fibers. Since the closed electromotive surfaces produced were not of symmetrical shape, it is difficult to believe that the observed cancellation could be produced by any but a uniform distribution of electromotive forces.

Examples of closed electromotive surfaces in heart muscle. The resemblance between the cardiac resting cell and a closed electromotive surface is well known. In this instance the cell has a uniform difference in potential of 90 mv. across its membrane and no difference in potential is measurable outside the resting cell, even when electrodes are adjacent to the cell. Durrer[a]

postulates that the inner layer of the myocardium is laced with rapidly conducting Purkinje fibers which give rise to an activation wave in the epicardial direction and also to the endocardial direction. If this is the case such activity would be an example of a closed electromotive surface and thus would not be measurable by any combination of externally applied leads. Another example would be extrasystoles which arise wholly within the myocardium. Initially they would not have boundaries on the epicardial or endocardial surfaces and until propagated to the ventricular surface would not be recorded in external leads.

Summary

Propagated wavefronts were produced by mechanical stimulation at points located deeply within the myocardium and the external field so produced was measured by electrodes located within a radius of 10 mm from the centrally stimulated point. In 104 experiments in 10 dogs the external field so produced was negligible until propagation reached either the epicardial or endocardial surfaces. If it is assumed that propagated intramural activity is temporarily a closed electromotive surface then the data presented suggest that there is a uniform difference in potential across this surface. Since there is no fundamental difference in the wavefront characteristics of closed electromotive surfaces and those which present boundaries on the epicardial or endocardial surfaces these data strongly suggest that there is a uniform difference in potential across all propagated wavefronts in normal ventricular muscle.

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Competitive idiocardiac and extrinsic pacemaker stimuli in heart block

I. Richard Zucker, M.D.
Edwin L. Rothfeld, M.D. *
Victor Parsonnet, M.D. ***
Lawrence Gilbert, M.D. *
Arthur Bernstein, M.D. *****
Newark, N. J.

Increasing use of electronic pacemakers in the treatment of heart block has stimulated interest in the electrophysiologic responses to these devices and their relationship to the intrinsic nervous system of the heart. Competition between extrinsic pacemaker stimuli and the sinus pacing mechanism of the heart has resulted in bizarre electrocardiographic findings.

As a result of these circumstances, the following questions have arisen: Do extrinsic pacemakers behave in a manner similar to that of the intrinsic pacemaker and its conduction system in relation to the refractory period and vulnerable phase? Can external pacemaker stimuli elicit serious arrhythmias if they occur in the vulnerable phase of the preceding beat? Do extrinsic pulse generator impulses that fall in the relative refractory period of the preceding beat elicit a subpar response?

Methods

Laboratory. Two dipolar catheters were introduced under fluoroscopic visualization into the right ventricle by way of the right external jugular vein of 30 anesthetized mongrel dogs. The external leads of each of the catheter probes were connected to separate external pulse generators. Electrical impulses in increasing voltages to a maximum of 15 volts, at various rates from 45 per minute to 120 per minute, and of 2 milliseconds duration were supplied to one dipolar catheter. Similar electrical impulses at varying rates, voltages, and of 2 milliseconds duration were supplied to the second dipolar catheter in deliberate competition with the other extrinsic pacemaker. Both competing external pulse generator stimuli were delivered to the heart in competition with the sinus pacemaker impulses.

Clinical. Patients who have intermittent or complete heart block with syncope are treated temporarily with a transvenous intracardiac dipolar electrode prior to operation for implantation of a pacemaker or for correction of defects in a pacemaker system.[1] After implantation of a perma-

From the [illegible] Department, Beth Israel Hospital, Newark, N. J.
Received for publication March 11, 1964.
[illegible] Department and Chief, Cardiac [illegible] Laboratory, Beth Israel Hospital. Address: [illegible] Ave., South Orange, N. J. [illegible]
*[illegible] Beth Israel Hospital.
**[illegible] Surgery, Beth Israel Hospital.
***[illegible] Thoracic Surgery, Beth Israel Hospital.
*****[illegible] Medicine, Beth Israel Hospital.

nent pacemaker the electrode is removed. In those patients with intermittent heart block occasional reversion to regular sinus rhythm results in competition between the sinus node and extrinsic pacemakers. Patients with complete heart block who have been treated with an implanted permanent pacemaker may experience an intermittent failure of the implanted pulse generator. On protection with the temporary transvenous dipolar electrode, competition occurs between the intermittently failing permanently implanted pulse generator and the temporarily protecting transvenous electrode. Other patients with intermittent heart block who have been treated with an implanted pulse generator may experience failure of the implanted pacemaker. At the time of the insertion of the temporary transvenous electrode, there may be a fortuitous competition between the sinus node, the temporarily functioning intermittently failing implanted pulse generator, and the transvenous electrode. In these instances pacemaker competition will result between the intrinsic and extrinsic pacemakers in patients with intermittent heart block, between two extrinsic pacemakers in patients with complete heart block, and between the intrinsic pacemaker and two extrinsic pacemakers in those patients with intermittent heart block and a faltering implanted pulse generator.

In a series of 40 patients with heart block in whom pacemakers had been implanted, competition of pacemakers was noted in 9 patients. In 4 patients with intermittent heart block there was competition between a sinus node mechanism and the implanted pacemaker. In 4 patients with complete heart block there was competition between the implanted pacemaker and the transvenous electrode. In 1 patient with intermittent heart block there was competition between the sinus node, a faltering implanted pacemaker, and the transvenous electrode.

Results

Laboratory. Fig. 1 shows two strips of Lead II recorded in a dog at two different times. The upper strip demonstrates competition between the normal sinoatrial pacemaker and two extrinsic pacemakers. The sinoatrial node discharges at a rate of 136 per minute. The P-P interval is 0.44 second and impulses originating from it are labeled number *1*. External pacemaker stimuli labeled *2* are discharged at a rate of 100 per minute and those numbered *3* occur at a rate of 130 per minute. In the upper tracing the extrinsic pacemakers produce the first five QRS complexes. The sixth is a fusion beat between an impulse originating in the sinoatrial node and one fired by one of the extrinsic pacemakers. The next eleven QRS com-

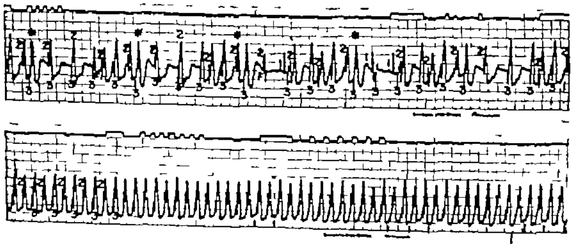
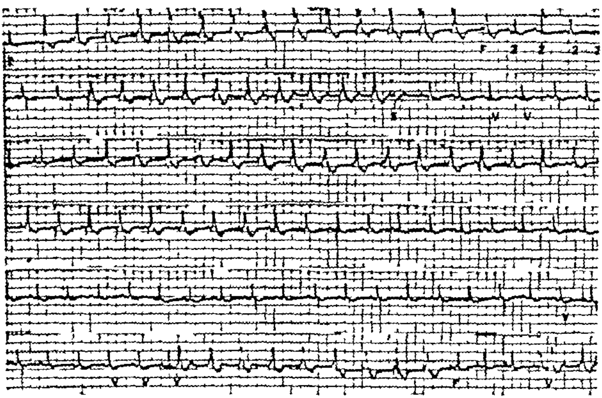


Fig. 1. Electrocardiogram recorded in a mongrel dog exhibiting competition between the sinus pacemaker and two extrinsic electrical pacemakers.



F Electrocardiogram in a patient with intermittent heart block exhibiting competition between the sinus pacemaker and extrinsic electrical pacemaker

plexes are in response to external pulse generator stimuli. The eighteenth QRS is a fusion between extrinsic and intrinsic stimuli. The next beat is conducted normally without interference. The twenty-sixth cycle has a longer P-R interval than the others because the P wave falls in the relative refractory period of the preceding beat. The next cycle shows normal conduction. A normal P wave seen in the S-T segment of the thirty-fourth QRS complex is not conducted because it falls in the absolute refractory period. The starred QRS complexes (3, 10, 1 25) follow the pacemaker impulse after a period of delay because they fall in the relative refractory period of the preceding cycle.

In the lower tracing the extrinsic pacemakers have captured the ventricles and have blocked effectively all stimuli arising in the sinoatrial node. Both external pacemakers numbered 2 and 3 are firing at a rate of 1 0 per minute. In effect the extrinsic stimuli produce a ventricular rate of 260 per minute. P waves occurring at a rate of 140 per minute are seen regularly but fail to capture the ventricles. This then is somewhat analogous to a bifocal ventricular tachycardia.

Clinical Fig. 2 is a continuous recording of Lead II in a patient with intermittent heart block demonstrating competition between a sinoatrial and an extrinsic pacemaker. In the top strip beats numbered *1* represent those fired by the extrinsic pacemaker whereas those numbered *2* are of sinoatrial origin. *F* denotes fusion beats between the extrinsic and intrinsic pacemakers. *S* is a subpar beat because it falls in the relative refractory period of the preceding beat. V indicates stimuli in the vulnerable period of the preceding beat. There is alternating capture of the ventricles by both pacemakers. This occurs when the rate of the sinoatrial node and that of the extrinsic pacemaker are similar allowing for fortuitous capture by the sinoatrial impulse when the extrinsic impulse slows slightly. This interplay results in multiform fusion beats. Stimuli falling in the vulnerable period of the preceding beat do not produce serious arrhythmias.

Fig 3 is a continuous recording of Lead II in a patient with complete heart block and two extrinsic pacemakers. Beats fired by the faster pacemaker are numbered *1* whereas those at the slower rate are numbered *2*. *R* indicates reciprocal beats probably produced by re-entry of the preceding impulse. *X* is an impulse that was not conducted because it falls in the absolute refractory period of the preceding beat. The remainder of the description is the same as in Fig 1. In general, most of the QRS complexes originate from the faster pacemaker. The slower stimulus captures the ventricles only when it falls propitiously beyond the refractory period of the faster pacemaker. The situation here is analogous to interference dissociation between two intrinsic foci. The extrinsic pacemakers behave in a fashion similar to the intrinsic foci in regard to refractoriness and fusion phenomena; however, extrinsic stimuli do not elicit serious arrhythmias when they fall in the vulnerable phase of the preceding beat.

Fig 4 is a continuous recording of Lead II in a patient with intermittent heart block and two extrinsic pacemakers. Complexes numbered *1* are of sinoatrial origin and those numbered *2* and *3* are discharged by the extrinsic pacemakers. *B* indicates beats originating in the sinoatrial node but demonstrating impaired A-V conduction (prolonged P-R interval) because the stimulus falls in the relative refractory period of the previous cycle. This complex arrhythmia demonstrates the intricacies that may arise when three pacemakers compete for control of the heart. There are multiform fusion beats, nonconducted stimuli, and impulses conducted in a subpar manner.[8] Stimuli falling in the vulnerable phase of the preceding cycle fail to produce arrhythmias.

In the 9 patients of the entire series there were 67 patient months of continuous competition. Pacemaker competition demonstrated in the laboratory and observed clinically did not result in serious ventricular arrhythmias when stimuli appeared in

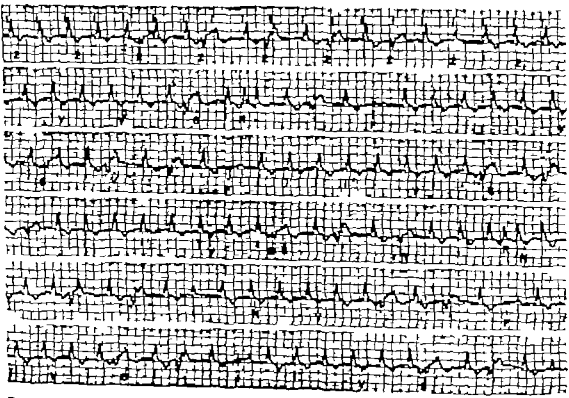


Fig 3 Electrocardiogram in a patient with complete heart block exhibiting competition between two extrinsic electrical pacemakers

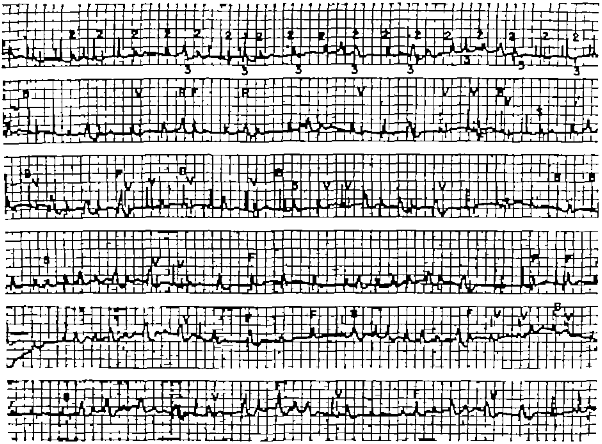


Fig. 4. Electrocardiogram in a patient with intermittent heart block exhibiting competition between the sinus pacemaker and two extrinsic electrical pacemakers

the vulnerable phase of the cardiac cycle There was no ventricular response to stimuli of the highest pacemaker voltage in the absolute refractory period Stimuli appearing in the relative refractory period elicited a subpar response

Discussion

Direct current impulses of the implanted pacemaker system are 2 milliseconds in duration with a driving voltage of 6 to 8 volts Patients have been driven with as much as 15 volts without incident Effective thresholds of stimulation have varied from less than $\frac{1}{4}$ volt to slightly less than 3 volts In no case had sufficient voltage been introduced at any part of the cardiac cycle to induce ventricular fibrillation or tachycardia We have seen transient interruptions in rhythm when the intracardiac dipolar electrode was introduced Mechanically induced arrhythmias were seen when the tricuspid valve was crossed or when the intraventricular septum was touched There was no change in rhythmicity on the disappearance of the mechanical contact stimuli and on the introduction of electrical stimuli by way of the transvenous intracardiac dipolar electrode

The refractory period of heart muscle is of sufficiently long duration to prevent a sustained tetanic contraction The absolute refractory period is present when no stimulus regardless of its amplitude will produce a response During the relative refractory period muscle excitability reappears and during this phase a stimulus will elicit a response depending on its strength and the degree of recovery of excitability The rhythmic alternation of the periods of excitability and refractoriness results in contraction and relaxation of the heart in a regularly recurring cycle

An interval at the end of systole ap-

proximately at the beginning of the down slope of the T wave of the electrocardiogram has been referred to as the vulnerable phase. Linenthal and Zoll[4] quantitated a supernormal period of hyperexcitability in 9 patients with competition between external and internal pacemakers without any difficulty or experience with ventricular fibrillation. It has been suggested that at this time the myocardium is hyperexcitable, and a single strong electrical shock may induce a serious derangement in the ventricular rhythm.[5]

Ventricular fibrillation may be produced by the introduction of a sufficiently strong stimulus 10 to 20 times higher than that required to produce a contraction. A stimulus of much less amplitude in the range of pacemaker driving voltage may induce ventricular fibrillation if it is of prolonged duration.[6] Widmon[7] established the mean threshold of ventricular fibrillation in dogs to direct current of 2 milliseconds duration at 35 milliamperes and 14 volts. In myocardial anoxia as well as during the administration of sympathomimetic amines fibrillation thresholds will be lower.

In order to explain why stimuli originating from an external pacemaker do not produce serious arrhythmias when they fall in the vulnerable period, we have postulated that the heart does not behave as a single vulnerable muscle mass. Instead we have considered the possibility that individual myocardial fibers are in different stages of repolarization at any given time. Because stimuli fired by external pacemakers are of short duration and relatively low current strength, they may not involve enough vulnerable fibers to produce ventricular tachycardia or fibrillation. However, ventricular fibrillation will occur if a stimulus of sufficient magnitude and duration falls in the vulnerable phase.

Conclusion

Electrocardiographic evidence is presented to illustrate competition between as many as three pacemakers. It has been demonstrated in dogs and observed in patients that multiple pacemaker stimuli appearing in any part of the cardiac cycle do not result in ventricular tachycardia or ventricular fibrillation. The highest voltage of an implanted pacemaker does not elicit a myocardial response in the absolute refractory period. Subpar responses are seen in the relative refractory period.

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A closed-end catheter for angiography using the percutaneous technique

*William J. Rawls, M.D.**
*Wade H. Shuford, M.D.***
*Eric L. J. Penfold, A.I.S.T.****
*Robert C. Schlant, M.D.*****
Atlanta, Ga.

The Seldinger technique of percutaneous catheterization is being used with increasing frequency to introduce catheters into the great vessels and cardiac chambers for diagnostic studies including selective angiography.[1] The technique has many advantages, but one of the disadvantages has been an increased risk of pressure injection angiography.[2-1?] Since the technique requires an open end catheter, much of the injectate leaves the catheter through the end opening as a forceful jet stream when a pressure injection is made. This jet may cause injury to the vessel or chamber wall, including dissection of the arterial wall, subendocardial infiltration, and myocardial perforation. Because of these complications we have developed a simple device which plugs the end opening but allows the injectate to leave the catheter through multiple side holes, giving a satisfactory rapid injection of contrast material without the adverse jet effect. Basically, our apparatus occludes the end opening of the catheter with a metal plug which is anchored to the proximal end of the catheter by a small metal wire.

Construction of occlusive plug. The occlusive plug is a drop of silver solder bonded to the end of a stainless steel wire constructed in the following manner. The tip of the wire (Table 1 *a*) is cleaned and coated with a stainless steel flux (Table 1 *b*). The silver solder (Table 1 *c*) is melted and allowed to drop onto a smooth, clean surface. The wire is then plunged into the droplet. When the solder had cooled, it is filed and polished to the desired diameter on a small jeweler's lathe (Fig. 1). We have used a stainless steel wire 0.018 inch (0.5 mm.) in diameter with an occlusive plug 0.050 inch (1.3 mm.) in diameter and found

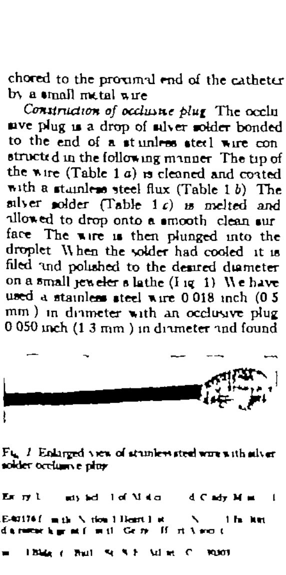


Fig. 1. Enlarged view of stainless steel wire with silver solder occlusive plug.

From the Department of Medicine and Radiology, Emory University School of Medicine, and Grady Memorial Hospital, Atlanta, Ga. [illegible]

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*Address [illegible] Thomas K. C[illegible] Memorial Bldg., [illegible] Butler St. S.E., Atlanta, Ga. 30303.

**Associate Professor of Radiology.

***Instructor [illegible] M. I.

****Associate Professor of Medicine.

it to be satisfactory for most of our catheters. The length of the wire can be varied to fit the catheter being used.

Description of technique Catheters for this technique should have a tapered end with an end opening 0 025 to 0 045 inch (0 6 to 1 1 mm) in diameter and with 4 to 6 side holes in the distal 0 5 to 2 0 inches (1 2 to 5 0 cm). A Cope adapter (Table 1 *d*) is attached to the catheter (Fig 2). If the catheter has a flared proximal end the Cope adapter can be attached as in Fig 3. If the catheter has a permanent female fitting the Cope adapter can be rearranged and with a male Luer Lok to male Luer Lok adapter (Table 1 *e*) can be attached to the catheter as in Fig 4. A stopcock is placed on the side opening of the Cope adapter.

Prior to introduction of the catheter into the vessel the length of wire needed to reach from the distal tip of the catheter to the proximal end of the Cope adapter is measured by advancing the wire into the catheter and lodging the plug in the tip distal to the side holes. A needle stop (Table 1 *f*) is passed over the wire and clamped at the point at which the wire emerges from the Cope adapter (Figs 2 3 and 4). The wire with the occlusive plug is then removed from the catheter and the catheter is introduced into the appropriate vessel using the usual Seldinger percutaneous technique. After the catheter has been placed in the vessel or chamber into which the injection is to be made the wire is inserted into the catheter through the Cope adapter and advanced to the distal end of the catheter. The proximal end of the Cope adapter is tightened until there is no leakage around the wire and the wire is secured with the needle stop so that it will not slip. Contrast material can then be injected through the side opening of the Cope adapter using a pressure apparatus.

Discussion

In 55 cases of adult cardiac catheterization we have used this technique to make 86 radiologic studies with pressure injections of contrast material. Each chamber of the heart and most of the major vessels have been used as a site of injection. In the patients studied to date no dissection of the arterial wall, subendocardial staining or myocardial perforation has been detected on serial rapid sequence films or during fluoroscopy immediately after angiography. The incidence of premature ventricular beats during ventriculography has been appreciably reduced. We have observed no other arrhythmias but would expect the incidence to be the same as when a closed end catheter of equivalent size is used.

The occlusive plug can be constructed to

Table 1

	Item	Manufacturer	Address	Catalog Number
a	Stainless steel wire medical grade spring temper Type 302	H K Porter Co Inc Alloy Metal Wire Works	Prospect Park P	
b	Airco d Flux for silver brazing Formula No 12	Airco Atlanta Welding Supply Air Reduction Sales Co	736 Hemphill Ave N W Atlanta Ga 30318	904 1250
c	Airco d 50 brazing alloy	Airco Atlanta Welding Supply Air Reduction Sales Co	736 Hemphill Ave N W Atlanta Ga 30318	925-5042
d	Cope adapter	Becton Dickinson and Company	Rutherford N J	N3016
e	Male Luer Lok to male Luer Lok adapter	Becton Dickinson and Company	Rutherford N J	MLL/MLL
f	Needle stop	Becton Dickinson and Company	Rutherford N J	418S
g	Gemma Teflon catheter	United States Catheter and Instrument Corp	Glens Falls N Y	TSP 35

fit a catheter of any size It is best to use a large lumen catheter that is tapered and has an end opening smaller than the occlusive plug When the wire is in place the reduction in the size of the lumen is small for example when a wire 0 018 inch in diameter is used with a No 8 5 F standard wall catheter the cross sectional area is reduced to that of a No 8 F catheter With catheters that have a lumen diameter of 0 056 inch (i e No 7 F thin wall or No 8 F standard wall) or greater this reduction does not require alteration of technique in order to obtain a satisfactory injection If one uses catheters that have lumens of smaller diameter the reduction in size is more appreciable Our experience with small catheters is limited but using a No

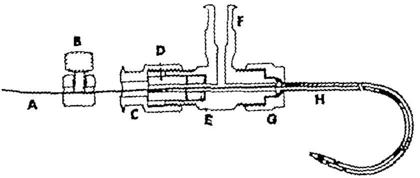


Fig 2 Cross section diagram of Cope adapter showing stainless steel wire with occlusive plug in tip of catheter A Stainless steel wire with occlusive plug on its distal tip B Needle stop C Removable female Luer Lok connector from Cope adapter D Metal gland from Cope adapter E Rubber gasket from Cope adapter F Body of Cope adapter G Removable flare type connector from Cope adapter H Catheter with flared proximal end I Male Luer Lok to male Luer Lok adapter J Catheter with female Luer Lok fitting

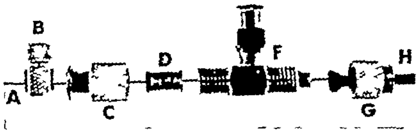


Fig 3 Disassembled Cope adapter with stainless steel wire and occlusive plug needle stop and catheter with flared proximal end (For key to parts see legend to Fig 2)

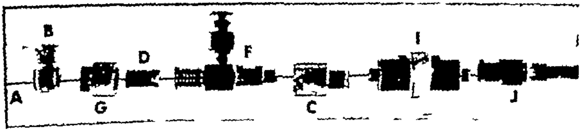


Fig 4 Disassembled Cope adapter rearranged to accommodate a catheter with a female Luer Lok fitting Note that parts C and G have been reversed and that I has been added (For key to parts see legend to Fig 2)

5 F thin walled catheter (lumen diameter of 0 034 inch or 0 86 mm) we have obtained satisfactory contrast angiograms by increasing the injection pressure by 50 per cent

The possibilities that the wire might break or that the solder plug might be dislodged from the wire during the pressure injection have been investigated The stainless steel wire used had an official tested tensile strength of 318 000 pounds per square inch (p s i) For a wire 0 016 inch in diameter this would correspond to 80 pounds of tensile strength In our laboratory we have measured the static weight which can be exerted on a solder plug 0 030 inch in diameter bonded to a stainless steel wire 0 018 inch in diameter and found it to be 70 pounds The solder plug did not separate from the wire but the wire in each test broke several millimeters proximal to the plug Therefore the strength of the wire and not the silver solder nor the solder wire bond is the limiting factor The decrease in tensile strength of the wire after the solder plug is attached is probably due to changes induced by heat during the soldering process If this wire with an occlusive plug were used in a properly constructed catheter it could withstand pressure injections calculated to be in excess of 10 000 p s i Our pressure injections in patients have never exceeded 300 p s i but in the laboratory we have injected water using 800 p s i through a 100-cm No 8 F Gensini TSP 35 Teflon catheter (Table 1 *f*) without damage to the wire

Summary

A simple inexpensive apparatus has been described for occluding the end of a catheter to be used for pressure injection angiography after the catheter has been introduced using the Seldinger percutaneous technique By using this apparatus and technique one has the advantage of both percutaneous catheterization and pressure injection angiography with a closed-end catheter

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Distribution of body sodium, potassium, and water and the excretion of aldosterone in dogs with spontaneous heart failure

*Goran E. Boys, M.D.**
*Hadley L. Conn, Jr., M.D.***
Philadelphia, Pa.

Spontaneous heart failure has been noted in approximately 14 of every 1,000 dogs examined in a veterinary cardiac clinic. The most frequent causes are congenital heart disease, heart worms, and a disease of unknown etiology that produces mitral insufficiency. The latter is of interest in that the valvular fibrosis and many of the clinical aspects have their counterpart in rheumatic mitral valvular insufficiency in man. When heart failure develops, these dogs with mitral insufficiency have been found to have abnormalities of cardiac hemodynamics and renal electrolyte excretion resembling those in human heart failure. Except for three measurements (one control) of plasma volume and one measurement of aldosterone secretion,[1] the distribution of body fluid and electrolytes and the aldosterone response have not been evaluated. The present data constitute a report of such measurements in a study of 12 dogs with mitral valvular insufficiency; 10 studies were made during the state of congestive heart failure and 11 during the compensated state. The results indicate highly significant increases in plasma volume, red-cell mass, extracellular volume and sodium content, and urinary excretion of aldosterone such as characterize congestive heart failure in man. In addition, the data show a small increase in serum potassium and decrease in cell potassium concentration of borderline statistical significance. Small and statistically nonsignificant increases in cell water and cell sodium concentration are noted.

Experimental material

Twelve dogs were studied. A clinical protocol for each animal is included in the Appendix. Ten of the 12 were relatively old, ranging from 5 to 14 years of age. Two were approximately 1 year of age. The diagnosis of mitral valvular insufficiency and of heart failure was based on clinical evaluation, catheterization studies, and in 7 instances on postmortem examination. In all cases the history included dyspnea, cough, unwillingness of the animal to lie down, and subsequent swelling of the abdomen and legs. The physical findings regularly included an apical systolic

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From the Robinette Foundation, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
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*Present address: Department of Medicine, University of Göteborg, Sahlgren's Hospital, Göteborg, Sweden.
**Robinette Foundation, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

murmur cardiomegaly pulmonary rales distended superficial veins and evidences of ascites and peripheral edema (See Fig 1) In 4 animals 2 with atrial fibrillation a very rapid ventricular rate (200 to 300 per minute) was noted and appeared to have precipitated heart failure The cardiomegaly and the pulmonary congestion of left heart failure were corroborated by chest roentgenograms Cardiac catheterization was carried out in 6 animals and revealed elevated end diastolic pressures in both ventricles and elevated mean pressure in both atria Angiography revealed the presence of a mitral regurgitant jet

Postmortem study of the dogs which died in the clinical state of congestive heart failure regularly revealed fibrosis and loss of substance of the mitral valve (Fig 2) biventricular enlargement left atrial enlargement pulmonary edema chronic passive congestion of the liver ascites and peripheral edema Inconstant findings were a regurgitant jet lesion of the left atrial endocardium fibrosis of the tricuspid valve and hydrothorax

All animals were maintained at cage rest in the presence of clinical heart failure Digoxin was administered routinely A fixed diet with constant normal intake of sodium was given Chlorothiazide diuretics were administered to 4 animals whose edema failed to disappear after digoxin therapy and cage rest With this therapeutic regimen it was possible to attain a state of clinical compensation in 10 of the 12 animals In the first 6 animals studies were made in the states of compensation and of heart failure so that each served as its own control In 2 instances (Dogs 7 and 8) the therapeutic regimen was inadequate to control edema so that no studies of the compensated state could be carried out In 4 cases (Dogs 9 10 11 and 12) immediate therapy was considered to be mandatory to permit survival and no studies were made during the initial episode of congestive heart failure Clinical compensation was achieved and studies were made during this state However it proved impossible despite termination of therapy and the addition of salt supplements and heavy exercise to reproduce heart failure As a conse



Fig 1 Dog with typical appearance of congestive heart failure due to mitral insufficiency Note the distended neck veins swollen abdomen due to ascites and the edematous paws



Fig 2 Heart of dog dying with the typical lesions of mitral insufficiency of undetermined etiology Note the thickened fibrosed mitral valve and chordae tendineae loss of valve substance thick walled enlarged left ventricle and the enlarged left atrium with a regurgitant jet endocardial lesion (MacCallum patch)

quence only studies of the compensated state were made in these 4 animals.

The studies designated as *congestive heart failure studies* were performed at a time when body weight was significantly in excess of the dry state, venous pressure was measurably elevated, and peripheral edema with or without ascites was present. The studies designated as *compensated state studies* were performed at a time when no clinical symptoms and signs of cardiac failure were present and when body weight could not be further reduced by continuation of the antidecompensative regimen.

Experimental measurements and calculations

Measurements included chromium 51 red cell mass,[4] sulfate (S^{35}) space as a measure of extracellular volume,[5] 6 hour tritium space as a measure of total body water,[6] 24 hour exchangeable sodium 24 and potassium 42,[7] and 24 hour urinary excretion of aldosterone[8] based on duplicate analyses of pooled 4 day collections of urine.

The chromium 51 labeled red cells, sodium 24, and tritium were given intravenously on the same day and their distribution was measured. If the animal maintained an essentially constant body weight and circulatory state as assessed clinically, the potassium-42 and sulfate 35 were similarly administered 1 week later. The animals were then treated until a steady compensated state was achieved, usually for a period of 2 to 6 weeks. The studies were then repeated in the same sequential fashion.

Chromium 51 labeled red cells were injected over a period of 2 to 3 minutes, the sulfate 35 over a period of 10 minutes, and the other isotopes over longer periods of from 20 to 30 minutes. Samples of blood were drawn into heparinized plastic syringes. Extreme precautions were used to avoid hemolysis. Samples of blood and urine were obtained at intervals of $\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 4, 6, 12, and 24 hours after initial injection of isotope. Serum, red-cell, whole blood, urine, and injected isotope aliquots were then analyzed for radioactivity. The concentration of chromium 51 in red cells and the concentration of sodium 24 and potassium-42 in serum were determined in a well type of scintillation counter with sodium iodide crystal. Gamma ray activity of these isotopes was determined with a sample shielded so that no beta ray activity from these or from the S^{35} or H^3 isotopes was recorded. Similar determinations were made on urine. Determinations of tritium and of S^{35} concentrations in serum and urine were made by beta counting in the Packard liquid scintillation counter. The latter determinations were made after an appropriate lapse of time to permit essentially complete decay of sodium 24 and potassium 42 activity, thus eliminating interference from these isotopes.

Plasma volume was determined from the red cell mass and venous hematocrit. No correction was made for the differences in venous and total body hematocrit (0.91) or the proportionate decrease in total body hematocrit in heart failure (0.86).[9]

Serum sodium and potassium concentrations were measured on the flame photometer with the use of a lithium internal standard. Extracellular sodium and potassium concentrations were estimated from the serum concentrations. No corrections were made for the Donnan effect or for the difference in plasma extracellular protein concentration since the two factors approximately offset each other. Extracellular sodium and potassium content was then calculated as the product of extracellular space and the appropriate cation concentration. Intracellular water was calculated as the difference between total exchangeable water and that calculated as being in the extracellular space. *Intracellular potassium and sodium content* were similarly calculated as the difference between the total exchangeable value and that for the extracellular space. Intracellular concentrations of sodium and potassium were calculated as the intracellular content of the appropriate cation divided by the intracellular water volume. In order to give the volume data a common reference standard for all animals and for both experimental states, red-cell mass, plasma volume, blood volume, extracellular water volume, and cell water volume are expressed in liters per kilogram (L./Kg.) of estimated or subsequently

observed dry weight. The differences of the means for the various results in the compensated and heart failure states were analyzed for statistical significance. For the entire group of animals the method employed was that of group comparison.[19] The differences were also analyzed for statistical significance in Dogs 1-6 by the method of individual comparison. In those animals in which two studies were made during either experimental state (Dogs 1 and 2) the results were averaged and included in the analyses without added weight.

Results

I. Blood. Both red cell mass and plasma volume were consistently increased in the decompensated animals. Red-cell mass and plasma volume were increased both with respect to the compensated state value in the same animal and with respect to mean value for the compensated group. Red cell volume in heart failure averaged 0.060 L./Kg., an increase of 82 per cent over the value of 0.033 L./Kg. found during compensation. Plasma volume averaged 0.077 L./Kg. in the decompensated animals, an increase of 60 per cent over the mean value of 0.048 L./Kg. found in the compensated animals. Calculated total blood volume was consequently increased in a similarly consistent manner due almost equally to excess red cell mass and plasma volume. The mean increase in blood volume was 69 per cent. All increases were highly significant ($p < 0.001$, < 0.005 and < 0.005 respectively).

The concentration of sodium in serum was not outside normal limits for the dog except in Dog 1. In one study this animal showed modest hyponatremia both in the failure state and in the ensuing compensated state. Over-all serum sodium concentration averaged 149 mEq./L. in failure and 150 mEq./L. in the compensated state. Serum potassium concentration was slightly (2 per cent) but consistently increased in cardiac failure from a mean of 4.63 to a mean of 4.71 mEq./L. An increase of similar magnitude was found in 5 of 6 animals in which the compensated state served as control for the decompensated state. None of these changes in cation concentration are of statistical significance when analyzed by group comparison ($p > 0.05$). However, if the changes in serum potassium concentration in the 6 animals serving as their own controls are subjected to analysis by individual comparison, the increase in serum potassium is found to be significant ($p = 0.05$).

II. Extracellular fluid. Extracellular water volume was consistently and markedly increased in heart failure when compared to the compensated state. Extracellular volume averaged 0.539 L./Kg. in failure as compared to 0.268 L./Kg. in the compensated state. This represents a mean increase of 101 per cent. With the assumption of equal serum and interstitial concentrations of sodium and of potassium, the experimentally obtained normal serum Na concentrations and the slightly increased potassium concentration lead to a calculated extracellular accumulation of these cations essentially of the same magnitude as the increase in extracellular water. The increases in total extracellular water, sodium, and potassium are statistically all very highly significant ($p < 0.001$).

III. Cells. During decompensation cell water was 0.481 L./Kg. of dry weight, an increase of 11 per cent over the mean value of 0.427 L./Kg. in the compensated state. Intracellular sodium concentration was calculated to be essentially the same during decompensation as during compensation, 26.5 vs. 26.4 mEq./Kg. of cell water. Intracellular concentration of potassium was calculated to be 6 per cent reduced during compensation, the mean value of 94.7 mEq./Kg. of cell water being comparable to a mean value of 100.4 mEq./Kg. in the compensated animal. No consistent directional change in the cell water or sodium concentration was observed in the 6 experiments in which the animal was used as its own control. The concentration of potassium fell in 4 of the 6 and was essentially unchanged in one other. Although none of these cellular alterations is statistically significant ($p > 0.05$), the change in the cell potassium of Dogs 1-6, analyzed by individual comparison, approaches significance ($p = 0.08$).

Despite negligible change and slight

fall in cellular concentrations of sodium and potassium respectively, the total intracellular amounts of both cations were modestly increased. These increases reflect the calculated greater (11 per cent) cell volume.

Urinary excretion of aldosterone. The excretion of aldosterone in the urine was consistently increased in heart failure in the 6 animals studied. Although the urinary excretion rates are only a fraction of the normal value for man (0.2 µg/Kg. per day), the mean value in heart failure is more than twice that in the compensated state. The excretion of aldosterone averaged 0.049 µg./Kg. of dry weight per day in heart failure as compared to 0.024 µg./Kg. per day for the compensated group. By individual comparison, the difference of the two means is highly significant ($p = 0.01$).

Experimental critique

Can the significant changes found be attributed to systematic experimental error rather than to biologic changes? To what extent is the failure to demonstrate significant changes in intracellular composition precluded by random experimental variation? In answer to the first question, we can only enumerate the major possible sources of error and point out that all abnormalities found, save those of intracellular composition, were of such great magnitude that they are beyond the range of recognized experimental error and therefore presumably reflect real biologic change. Whether use of more precise techniques would reveal statistically significant alterations of intracellular constitution in spontaneous heart failure remains to be established.

In order to avoid difficulties in differential radioisotope counting, complete evaluation of each experimental state was based on 2 studies 1 week apart. Although the therapeutic program was directed toward maintaining a steady state during this period, some alteration in fluid and electrolyte balance cannot be excluded. Another problem is posed by the desirability to reduce compartmental volumes to a common denominator. Although relation to ideal or actual dry weight is theoretically sound, it offers practical difficulties. Some animals which were rendered free of excess fluid rapidly regained weight through increases in lean body mass and others (Dogs 7 and 8) were never observed free of edema. In Dogs 3, 7, 8 an approximation of dry weight, admittedly biased, was made by assuming it to be equal to the existing wet weight less the excess of extracellular volume exceeding 20 per cent of estimated dry weight.

Other important considerations are the validity of the 24 hour exchangeable sodium and potassium results and the validity of equating the result of the sulfate space with extracellular volume. Measurements of 24 hour exchangeable sodium and potassium are usually reproducible as corroborated by our good agreement on repetitive measurements in Dogs 1 and 2. A minor error is introduced because complete exchange does not occur within 24 hours. Exchangeable potassium at this time has been calculated to be 80 to 100 per cent of total body potassium with an average of 90 to 95 per cent.[11] Twenty-four hour exchangeable sodium normally includes nearly all of the body sodium except that in bone. Only a small fraction of bone sodium is included.[1] Thus the extent of 24 hour exchangeability is normally not a major limitation except in evaluating changes in bone sodium. O'Meara's data[7] would suggest that the K, Na,[4] and H[3] equilibration periods used are adequate even in hydropic states, although K at 48 hours is preferable.

The sulfate space as reflected by a 30 minute equilibration period is generally considered to provide the most accurate estimation of extracellular volume in the normal subject, but is inapplicable in heart failure because of the much greater time required for equilibration of sulfate in plasma with that in the edema fluid in body cavities.[4,13] On the other hand, the exponential regression curve analysis method used here gives reasonable results in heart failure.[4] Other data obtained during this study provide one additional line of evidence which suggests that these values are acceptably correct. Under the assumption that ascites is the hydropic collection that requires the longest period for equilibration with plasma, the time required for equilibration of sul-

fate concentration in ascites with that of serum was determined in several animals. It was found to be about 6 hours. Extracellular volumes calculated from the 6 hour sulfate distribution (corrected for urinary and normal rate of extraurinary loss of sulfate from the extracellular space cumulative to this time) would then be expected to have essentially the same values as those derived from analysis of the curve of sulfate disappearance from the plasma. Such was the case.

The control values for plasma and blood volume and their increase in heart failure are presumed to be even greater than shown by our data. These values derive from a calculation in which venous hematocrit is substituted for total body hematocrit, the latter being unobtainable directly in the intact animal. Normally, total body hematocrit is about 0.91 of venous hematocrit and in heart failure about 0.86 of venous hematocrit.[9] Hence control plasma volume would be 9 per cent greater and plasma volume in heart failure about 14 per cent greater than shown in Table I.

Discussion

Dogs with mitral insufficiency in a state of cardiac compensation were found to have a body distribution and concentration of water, sodium and potassium similar to the findings in normal dogs and human beings. The blood volume of 8 per cent is essentially the same as the normal value; the extracellular volume of 26 per cent and the total body water of 69 per cent of body weight are somewhat higher than normal values.[7,19,11] Serum sodium concentration is the same as and serum potassium concentration only slightly higher (0.3 mEq./L.) than our laboratory values for normal dogs.

Of greater importance to the comparative cardiologist is the further evidence of common physiologic disturbances in spontaneously occurring heart failure due to mitral insufficiency in the dog and in untreated low output heart failure in man.

The correspondence in the two states of the cardiac hemodynamic abnormalities and of the renal electrolyte excretory pattern had been emphasized previously by Wallace.[8] Our data demonstrate increases in plasma volume, red-cell volume, blood volume, extracellular volume and sodium content and urinary excretion of aldosterone in canine heart failure that have a qualitative and semiquantitative identity with those reported in human congestive heart failure.[12,13]

A similar parallelism of intracellular composition is not established. In human heart failure an accumulation of cell water, increase in sodium concentration, and decrease in potassium concentration have been the usual findings.[12] Nevertheless the magnitude of the changes has rarely been subjected to statistical treatment for significance; changes in cationic intracellular concentration have not always been determined (our results indicate a decrease in the cell concentration of potassium despite a slight increase in the total mass of cell potassium) and even different patterns of change occasionally have been reported, including one report of calculated cellular dehydration.[4] Our reported 11 per cent gain in cell water, negligible gain in sodium concentration, and 6 per cent decline in potassium concentration do not reach levels of statistical significance, although the loss of potassium ($p = 0.08$) is suggestively close. Thus the only safe conclusion is that combined data on intracellular composition reveal no startling discrepancies between the responses to heart failure in dog and man.

The slight, borderline significant (see *Results*) increase in serum potassium concentration in heart failure leads to the speculation that a significant increase in serum potassium concentration might be revealed by more thorough analysis of the data from human beings in heart failure. A slight hyperkalemia might be attributed to either a minor defect in renal excretion of potassium or a reduction in the transcellular potassium gradient, or to both. Our concomitant finding of reduced concentration in cell potassium, if real, favors the latter process. Such redistribution of potassium might, in turn, be attributed to metabolic depression of active membrane transport of cations or to increased aldosterone effect.

The increase in the excretion of aldosterone in heart failure represents the sum of an increase in free and oxo-conjugated forms. The total values represent less

Table I

Dog No	*Status*	*Weight (Kg)*	*RCM (L)*	*PV (L)*	*BV (L)*	*RCM/EDW (L/Kg)*	*PV/EDW (L/Kg)*	*BV/EDW (L/Kg)*	*TBW (L)*	*ECW (L)*
1	C	38.5	1.51	1.71	3.22	0.039	0.044	0.084	30.8	11.2
	C	38.5	1.45	1.92	3.37	0.038	0.050	0.088	30.8	11.7
	F	47.0	2.40	2.50	4.90	0.062	0.065	0.127	36.0	20.0
	F	46.2	2.15	1.99	4.14	0.056	0.052	0.108	37.9	22.4
	C	18.6	0.58	0.88	1.46	0.031	0.047	0.078	15.2	5.8
	F	22.3	0.85	1.04	1.89	0.046	0.056	0.102	19.0	9.5
2	F	22.9	0.83	0.93	1.76	0.045	0.050	0.095	18.6	9.4
3	C	19.0	0.70	1.10	1.80	0.037	0.058	0.095	14.3	5.2
	F	19.4	1.24	1.72	2.96	0.081	0.081	0.162	15.2	9.2
4	C	16.2	0.58	0.86	1.44	0.036	0.053	0.089	12.0	5.3
	F	16.3	0.91	1.42	2.33	0.056	0.087	0.143	14.1	6.0
5	C	19.4	—	—	—	—	—	—	11.7	5.8
	F	3[illegible].1	1.28	2.09	3.37	0.066	0.108	0.174	22.9	10.5
6	C	5.6	—	—	—	—	—	—	3.6	1.3
	F	6.2	—	—	—	—	—	—	4.5	1.5
7	F	10.4	0.61	0.74	1.35	0.076	0.092	0.168	8.2	4.5
8	F	9.4	0.20	0.36	0.56	0.034	0.061	0.095	7.8	5.4
9	C	58.5	1.91	2.63	4.54	0.033	0.045	0.078	30.6	12.5
10	C	15.4	0.52	0.66	1.18	0.034	0.043	0.077	8.6	2.9
11	C	11.6	0.26	0.51	0.77	0.022	0.044	0.066	6.8	2.4
12	C	23.4	0.79	1.15	1.94	0.034	0.049	0.083	21.7	7.7
						C(8)	C(8)	C(8)		
						0.033	0.048	0.082		
						F(7)	F(7)	F(7)		
						0.060	0.077	0.137		
						(+82%)	(+60%)	(+67%)		
						<0.001	<0.005	<0.005		

*p value for mean difference [illegible] Dogs 1-4 by method of individual comparison (each serving as its own control).
†In milliequivalents per liter or kilograms.
C, Cardiac compensation. *F*, Congestive heart failure. *RCM*, Red-cell mass. *PV*, Plasma volume. *BV*, Blood volume. *EDW*, Estimated [illegible] exchangeable sodium. [illegible] 24-hour [illegible] exchangeable potassium. [illegible] Intracellular [illegible]

than 1 per cent of the total secretion of aldosterone measured by Carpenter in dogs with experimentally produced heart failure.[3] Thus the predominant amount would appear to be excreted in an unmeasured metabolized form. The extent of increase in the ratio of measured to unmeasured aldosterone and of such contribution to the increase in combined free and oxo-urinary aldosterone is unknown and presently under study. Other explanations seem to be more likely, although the increased excretion of aldosterone is not a result of low salt diet, which is known to stimulate the secretion of aldosterone, since our animals had a fixed normal intake

ECF / EDW (L/Kg)	CW (L)	CW / EDW (L/Kg)	Na (mEq/L)	Na (mEq)	Na † / CW	K (mEq/L)	K (mEq)	K † / CW	L Ald
0 291	19 6	0 509	140	2 160	30 2	4 0	1 590	78 8	0 034
0 304	19 1	0 496	154	2 250	23 5	4 9	1 560	78 7	
0 519	16 0	0 416	138	3 336	36 0	4 8	1 400	87 0	0 050
0 587	15 3	0 403	149	4 050	45 9	5 0	1 860	112 8	
0 312	9 4	0 505	149	1 072	16 8	4 4	1 000	103 6	0 019
0 311	9 5	0 511	152	1 481	3 9	4 9	1 007	101 0	
0 503	9 2	0 495	153	1 557	12 4	4 6	1 030	107 0	0 052
0 274	9 1	0 479	151	919	25 9	4 9	980	105 4	0 016
0 597	6 0	0 390	148	1 385	1 1	5 1	676	95 0	0 071
0 327	6 7	0 414	150	1 046	37 5	5 0	900	130 1	0 072
0 370	8 1	0 500	150	1 268	45 4	4 8	804	95 7	0 04
0 299	5 9	0 304	146	952	17 8	4 2	607	98 6	0 030
0 541	12 4	0 639	148	2 106	44 2	4 4	1 005	76 7	0 067
0 232	2 3	0 411	150	297	47 8	3 8	259	107 6	0 075
0 268	3 0	0 536	154	287	16 8	4 2	250	80 6	0 067
0 563	3 7	0 463	146	774	31 6	—	—	—	—
0 915	2 4	0 407	150	860	70 5	5 0	277	110 7	—
0 214	18 1	0 309	147	1 9 0	7 3	4 4	2 042	109 4	—
0 188	5 2	0 370	150	6	33 8	4 8	358	60 0	—
0 207	4 4	0 379	153	551	42 7	5 5	457	100 0	—
0 379	14 0	0 598	151	1 334	11 8	5 0	1 580	110 6	—
C (10)	C (10)	C (10)		C (10)	C (10)	C (10)		C (10)	C (6)
0 268		0 427	150		26 4	4 63		100 4	0 074
F (8)		F (8)	F (8)		F (8)	F (7)		F (7)	F (6)
0 539		0 481	149		26 5	4 72		94 7	0 049
(+101%)		(+11%)	±0%		±0%	(+2%)		(−6%)	(+104)
<0 001		>0 05	>0 05		>0 05	>0 05		>0 05	
						<0 05		0 08	0 01

dry weight ... kilograms TBW Total body water ECW Extracellular water CW Cell water Na Serum sodium ... 24 h ... L Ald 24-hour urinary ... of aldosterone ... micrograms per kilogram

of salt Translation of Carpenter's data would assign the result mainly to increased secretion of aldosterone via another form of stimulus probably the renin angiotensin mechanism[17] The presence of an advanced degree of hepatic congestion suggests that delayed degradation of aldosterone could be an additionally operative mechanism since it was previously described in the rat[18] Increased excretion of aldosterone in the presence of advanced heart failure does not necessarily indicate a central role for hyperaldosteronism in initiating cardiac edema In fact our preliminary unpublished data fail to show clear increases in the excretion of

terone during the initial stage of fluid collection. Such findings are similar to those reported for man by Sanders.[8]

Summary

A series of studies was made in the compensated and decompensated phases of spontaneously occurring canine congestive heart failure secondary to mitral insufficiency of undetermined etiology.

In 12 dogs results were obtained for body composition and distribution of water, sodium, and potassium and for the excretion of aldosterone.

The data show highly significant increases in plasma volume, red cell mass, extracellular water, and extracellular sodium content and in the excretion of aldosterone. Extracellular concentration of sodium and potassium remain normal, although serum potassium is increased slightly ($p = 0.05$) over that of the compensated state. Intracellular water is increased 11 per cent and intracellular potassium concentration is decreased 6 per cent. Although neither change reaches statistical significance, the latter is suggestively close ($p = 0.08$). *Intracellular sodium concentration varies considerably* but on the average is negligibly increased.

The results in the compensated animals approximate the results in normal man and dog. The pattern of response found in decompensation is virtually identical to the usual response to low output right heart failure in man.

We wish to express our appreciation to the members of the cardiac unit of the University of Pennsylvania Veterinary School, especially Dr. David Detweiler and Dr. Donald Patterson, for the cooperation and aid which they gave in the performance of these studies.

Appendix

Dog 1. A 6-year-old male Weimaraner. History of respiratory distress, ascites, and peripheral edema. Noted by local veterinarian to have atrial fibrillation. Physical examination revealed cardiomegaly, murmur of mitral insufficiency, and signs of congestive heart failure. Ventricular rate was controlled by digitalization and signs of decompensation disappeared slowly. Subsequent right heart catheterization and angiocardiogram revealed normal cardiac output, normal intracardiac pressures, and no cardiac shunt. A first control study was made. Cardiac decompensation was precipitated by withdrawal of digoxin plus treadmill exercise. Two studies during heart failure and one during a compensated period were made subsequently. Salt restriction and diuretics were not employed. Heart failure seemed to be closely related to exce[illegible]rdiac rate. Death was caused accidentally by the intravenous administration of guanethidine 3 mg per kilogram. Postmortem findings included microscopic areas of myocardial destruction with patent coronary blood vessels, moderate fibrosis and loss of substance of the mitral valve, a circular plaque of fibrosis of the left ventricle, an enlarged left atrium, chronic passive congestion of the liver, and anasarca.

Dog 2. A 1-year-old male boxer. History of ascites and peripheral edema. Physical examination revealed a murmur thought to reflect mitral insufficiency. Right heart catheterization showed elevated pressure throughout all chambers. Digoxin and cage rest permitted cardiac compensation and control studies were made. Salt restriction and diuretics were not employed. Two subsequent episodes of heart failure ensued, one spontaneous and one induced by exercise. Studies were made during two of these episodes. Death followed shortly after the intravenous administration of guanethidine 5 mg per kilogram. Postmortem findings included mitral insufficiency, ventricular enlargement, bilateral atrial dilatation, ascites, hydrothorax, and congestive hepatosplenomegaly.

Dog 3. A 5-year-old hound of mixed pedigree. History of respiratory distress, ascites, and peripheral edema. Initial physical examination was compatible with left ventricular hypertrophy, mitral insufficiency, and congestive heart failure. There was extreme (sinus ?) tachycardia at a heart rate of 250 per minute. Cardiac catheterization revealed markedly elevated right and left ventricular end-diastolic pressures. Angiocardiography revealed a normal pulmonary artery, generalized cardiomegaly, and mitral insufficiency. Treatment included digoxin, diuretics, and cage rest but no salt restriction. When indications of heart failure disappeared, control studies were made. Subsequently, two episodes of heart failure were reprecipitated by withdrawal of digoxin and studies were made during the first. Death occurred during the second recurrence of heart failure. Postmortem examination revealed severe fibrosis and loss of substance of the mitral [illegible]ve and, to a lesser extent, of the tricuspid valve. There were marked dilatation and little hypertrophy of both ventricles, pulmonary edema, ascites, chronic passive congestion of the liver, and peripheral edema.

Dog 4. An 8-month-old male coonhound. History of respiratory distress and ascites. Previous to admission to the veterinary hospital, abdominal paracentesis was performed with removal of 2,800 ml. of fluid and a therapeutic regimen of digitoxin and diuretics was started. Physical examination on admission revealed tachypnea, diffused scattered râles, a Grade 3 systolic murmur thought to represent mitral insufficiency, a diastolic gallop rhythm, and ascites. The electrocardiogram was compatible with left ventricular hypertrophy. Radiography showed marked biventricular and left atrial enlargement. Digitoxin was discontinued and the first studies were made with the animal in the de

compensated state. Digoxin and cage rest were then used as a therapeutic regimen and cardiac compensation was achieved. Dietary salt was not restricted. A second series of studies was performed with the animal in the compensated state. Subsequent right and left heart catheterization showed left ventricular and left atrial enlargement, right ventricular enlargement, and marked mitral insufficiency as demonstrated on the angiocardiogram. Intraventricular pressures during this state of compensation were normal. The animal is presently alive and well.

Dog 5. A 10-year-old male foxhound. History of coughing followed by ascites. Physical findings included lung rales and ascites and the murmur of mitral insufficiency. The heart appeared to be enlarged by radiography. The clinical diagnosis was left and right heart failure due to mitral insufficiency. Initial studies were done at this time. Digoxin and cage rest were then instituted with remission of the signs and symptoms of decompensation. A second study of body composition was then carried out. Cardiac catheterization was not performed. The animal is alive and well at the time of this communication.

Dog 6. A 13-year-old female fox terrier. History of respiratory distress and episodes of clinically diagnosed interstitial nephritis. Physical examination revealed the murmur of mitral insufficiency, rales in the lungs, respiratory distress, and minimal peripheral edema. The clinical diagnosis was mitral insufficiency with left heart failure and mitral right heart failure at the time of our study. Digoxin was administered with evidence of regression of collections of fluid. The second study during compensation was made at this time. Subsequently, decompensation reoccurred and the animal died suddenly. Postmortem findings revealed marked thickening and loss of mitral valve substance, jet lesion of the left atrial endocardium, bilateral cardiac hypertrophy and dilatation, passive congestion of the liver, and arteriosclerosis of the abdominal aorta.

Dog 7. A 5-year-old female terrier. History of coughing and abdominal distention. Physical examination showed signs of advanced heart failure of the right side and probable *mitral insufficiency*. Body composition studies were initiated promptly, but death occurred during the *first week after admission*. Postmortem findings revealed marked fibrosis and loss of substance of the mitral valve and to a lesser extent of the tricuspid valve. Other findings included biventricular hypertrophy and dilatation, hydropericardium, pulmonary edema, ascites, chronic passive congestion of the liver, and peripheral edema.

Dog 8. A 14-year-old male terrier. History of coughing and respiratory distress. Physical examination revealed Grade 3 murmurs attributed to mitral and tricuspid insufficiency. There were râles in the lungs, ascites, and peripheral edema. Radiography showed a very large heart thought to represent mostly left ventricular enlargement. Electrocardiogram showed many atrial premature beats. Therapy included digoxin, diuretics, potassium supplements, and cage rest, but not salt restriction. However, appetite was poor. Decompensation could not be controlled and the animal died during the decompensated state studies. Postmortem examination revealed severe fibrosis and loss of substance of the mitral valve, biventricular hypertrophy, pulmonary edema, ascites, hepatic congestion, and peripheral edema.

Dog 9. A 7-year-old male Newfoundland. History of marked gain in weight, respiratory distress, ascites, and peripheral edema. Physical findings suggested mitral insufficiency and atrial fibrillation with rapid ventricular rate. Electrocardiogram and left heart catheterization confirmed these diagnoses. The left ventricle and atrium were considerably enlarged. The ventricular rate was 200 per minute. After digitalization the ventricular rate slowed to 110 per minute and signs of decompensation disappeared. During a period of 2 years in the dog colony, two episodes of decompensation occurred when digoxin was stopped. However, during the course of the present studies withdrawal of digoxin, added dietary salt, and treadmill exercise failed to increase notably the ventricular rate and failed to induce signs of cardiac decompensation.

Dog 10. Old (age undetermined) female beagle hound. History compatible with dyspnea and orthopnea. Physical findings and radiographic findings were those of left heart enlargement and mitral insufficiency. Indications of left heart failure did not reappear during observation. Exhaustive exercise was added to the regimen, but decompensation could not be induced.

Dog 11. A 5-year-old female spitz. History of respiratory distress. Physical findings were compatible with mitral insufficiency. Left heart catheterization and angiocardiography revealed mitral insufficiency and modest left ventricular enlargement. Signs of cardiac failure did not reappear on cage rest. Exercise and dietary increments of salt failed to induce decompensation.

Dog 12. A 1-year-old male German shepherd. History of ascites, peripheral edema, and respiratory distress. Physical examination revealed the murmur of mitral insufficiency and a supraventricular tachycardia with a ventricular rate of 310 per minute. Radiographic studies showed general cardiac enlargement. Left heart catheterization revealed elevated atrial pressures. Mitral regurgitation was seen on angiocardiography. Treatment included digitalization and cage rest but no salt restriction. The cardiac rhythm changed promptly to atrial fibrillation with a slower ventricular rate and signs of cardiac decompensation regressed. Subsequently the rhythm reverted to normal sinus and no further signs of failure were noted. Studies of body composition were made at this time. Subsequently, exhausting exercise and dietary increment of salt failed to reproduce cardiac decompensation.

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In 12 dogs results were obtained for body composition and distribution of water, sodium, and potassium and for the excretion of aldosterone.

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Dog 2. A 4 year-old male boxer. History of ascites and peripheral edema. Physical examination revealed a murmur thought to reflect mitral insufficiency. Right heart catheterization showed elevated pressures throughout all chambers. Digoxin and captopril permitted cardiac compensation, and control studies were made. Salt restriction and diuretics were not employed. Two subsequent episodes of heart failure ensued, one spontaneous and one induced by exercise. Studies were made during two of these episodes. Death followed shortly after the intravenous administration of guanethidine, 5 mg. per kilogram. Postmortem findings included mitral insufficiency, ventricular enlargement, bilateral atrial dilatation, ascites, hydrothorax, and congestive hepatosplenomegaly.

Dog 3. A 5 year old hound of mixed pedigree. History of respiratory distress, ascites, and peripheral edema. Initial physical examination was compatible with left ventricular hypertrophy, mitral insufficiency, and congestive heart failure. There was extreme (sinus ?) tachycardia at a heart rate of 250 per minute. Cardiac catheterization revealed markedly elevated right and left ventricular end diastolic pressures. Angiocardiography revealed a normal pulmonary artery, generalized cardiomegaly, and mitral insufficiency. Treatment included digoxin, diuretics, and cage rest but no salt restriction. When indication of heart failure disappeared, control studies were made. Subsequently two episodes of heart failure were reprecipitated by withdrawal of digoxin and studies were made during the first. Death occurred during the second recurrence of heart failure. Postmortem examination revealed severe fibrosis and loss of substance of the mitral valve and to a lesser extent of the tricuspid valve. There were marked dilatation and little hypertrophy of both ventricles, pulmonary edema, ascites, chronic passive congestion of the liver, and peripheral edema.

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Observations on histochemical differential diagnosis between primary and secondary cardiomyopathies

Behavior of monoamine oxidase, phosphorylase, and glycogen in heart muscle

E. Bajusz, M.D., Ph.D.
*G. Jasmin, M.D., Ph.D.***
Montreal, Canada

It is known that by using conventional staining techniques no clear histologic distinction—except in some instances for a subendocardial localization of lesions—can be established between primary cardiomyopathies and those resulting from coronary occlusion in human and experimental autopsy material.[1] Thus, if coronary thrombosis is absent or hidden, any conclusion concerning possible etiological factors remains uncertain. In fact, morphologic differential diagnosis between primary (i.e., nonocclusive or metabolic) and secondary (i.e., occlusive or anoxic) necrotizing cardiomyopathies is one of the basic yet still unsolved aspects of cardiovascular pathology. This problem has recently come even more to the fore since it is increasingly recognized that some forms of clinical cardiac necrosis and interstitial myocarditis represent reactions to direct metabolic injury in hearts with a normal blood supply.[2]

The heart muscle is extremely rich in a number of oxidative and hydrolytic enzymes, and it had reasonably been assumed that alterations in the normal metabolic pathways, which lead to irreversible myocardial damage, might be recognizable in the early stage by studies on enzyme activities and/or on some vitally important metabolites. The application of histochemical techniques, however, did not fulfill this hope, mainly because most of the enzymatic changes recognized so far during the onset and development of myocardial lesions were already accompanied by, or merely followed, some gross structural abnormalities. This rather disappointing general conclusion can be derived from the earlier histochemical investigations performed partly in human material and partly in animal material, mainly after surgical occlusion of coronary arteries in the rabbit and dog. Moreover, in addition to possible species differences in reactivity, a more detailed evaluation of the scattered data in the literature is also hindered by variations in the techniques used in the experimental

From the Department of Pathology, Faculty of Medicine, University of Montreal, Montreal, Canada.
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Address: Department of Pathology, University of Montreal, P. O. Box 6128, Montreal, Quebec, Canada.
**Research Associate of the Medical Research Council of Canada.

conditions applied and in any unknown factors that might well have been involved especially when dealing with human necropsy specimens But even so it seems to be a common finding that a depletion of the stainable labile fraction of glycogen is the most readily detectable prenecrotic change in the ischemic myofiber (for literature see References 1 8 10) Curiously no attention was paid in these earlier studies to the behavior of enzymes partaking in glycogen metabolism during the early stages of myocardial damage neither was the question broached whether any of the histochemical techniques are of value from the point of view of differential diagnosis

The following report shows that in addition to a depletion of glycogen a decrease in or loss of the activities of phosphorylase and monoamine oxidase is also a definite prenecrotic alteration in certain types of necrotizing cardiomyopathies and that these three substances not only are very sensitive to potentially cardiotoxic influences but behave differently during the development of primary and secondary cardiomyopathies

Materials and methods

Three hundred and sixty female Sprague Dawley rats with an average initial body weight of 112 grams (range 90 to 128 grams) were used Except for those on the potassium-deficient diet all animals were maintained exclusively on the standard laboratory diet Purina Laboratory Chow and received tap water ad libitum Six different (three primary and three secondary) necrotizing cardiomyopathies were analyzed comparatively throughout their entire development by using histochemical and conventional staining techniques

Primary cardiomyopathies were induced by (1) injection of plasmocid (a now obsolete antimalarial metabolic inhibitor compound) (2) administration of dihydrotachysterol or DHT (a steroid of the vitamin D group) and (3) feeding of a potassium-deficient diet *Plasmocid* 6 methoxy 8 (diethylamino propylamino) quinoline dihydroiodide* was given intraperitoneally in a single dose of 3 0 mg in 0 3 ml of physiologic saline *DHT* (Calcamine*) was administered by stomach tube in a single dose of 1 5 mg in 1 0 ml of Mazola oil The *potassium deficient diet* (Low Potassium Diet†) was found to be also comparatively poor in magnesium it contained only 52 mg per kilogram of magnesium (which is close to the minimal daily requirement of rats[11])

Secondary cardiomyopathies were induced by (1) ligature of coronary artery (2) injection of methoxamine (a highly potent vasopressor amine) and (3) administration of metaraminol (another synthetic vasopressor compound) *Ligature of coronary vessels* was performed under light ether anesthesia by using the surgical procedure described in detail elsewhere[1] The left coronary artery was ligated about 1 mm below its origin *Methoxamine hydrochloride* (Vasoxyl‡) and *metaraminol bitartrate* (Aramine§) were injected subcutaneously in a single dose of 4 0 mg in 0 2 ml of physiologic saline

After the surgical intervention or the administration of the potentially cardiotoxic compounds the animals (always 4 rats at a time) were killed by decapitation at different intervals ranging from 1 minute to 96 hours In the case of the more slowly developing cardiac lesions induced by the potassium-deficient diet the animals were sacrificed at 24 hour intervals from the first day until the sixteenth day At autopsy transventricular ablation was rapidly performed (after which cardiac contraction ceases almost instantaneously) and the remaining lower two thirds of each ventricle was mounted on chucks frozen with liquid air and stored in a deep freezing cabinet at −70 C Serial sections were cut from each specimen on the same or the following day in a Pearse Cryostat at −20°C the thickness of the sections was always 10μ

The activity and distribution of *monoamine oxidase* was demonstrated with nitro BT after Glenner and associates[1] using tryptamine hydrochloride as substrate (incubation time 45 minutes) *Phosphorylase*

Courtesy of Dr R C Elderfield Department of Chemistry University of Michigan Ann Arbor Mich

*Wander A G
†Nutritional Biochemicals Co
‡Burroughs Wellcome & Co (Canada) Ltd
§Merck Sharp & Dohme of Canada Ltd

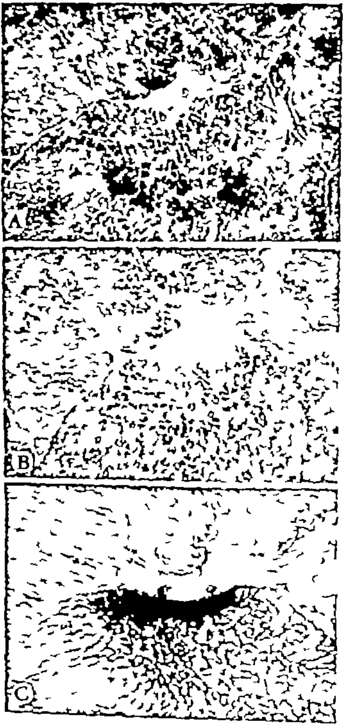


Fig. 1. Histochemical characteristics of the primary, nonocclusive type of necrotizing cardiomyopathy induced by plasmocid in the rat. *A*, Phosphorylase. A partial decrease in enzyme reaction in and increase around a subendocardial necrotizing focus 10 hours after injection of plasmocid. *B*, Monoamine oxidase. Decline in enzyme activity within the same degenerating area. Note that both phosphorylase and monoamine oxidase are only partially lost and not completely absent within the affected area. *C*, Leucine aminopeptidase (*black area*). The presence of this enzyme is indicative of proteolytic activities and its early appearance is characteristic of primary cardiac lesions.

was studied by applying the method of Takeuchi and associates[12,13] (incubation time 120 minutes) and *glycogen* was identified by its staining characteristics with the periodic acid Schiff (PAS) technique (on frozen sections after fixation with Rossman's fluid) and by its digestibility with diastase. For the purpose of routine morphologic studies the frozen sections were post-fixed with formalin and stained with hematoxylin phloxine saffron (HPS).

Results

Normal control hearts. The activity of *monoamine oxidase* was confined to the myocardial fibers, no reaction being seen in the interstitial tissues. The reaction for this enzyme was constantly positive in the control hearts; in the individual muscle fibers the formazan granules indicating the localization and activity of monoamine oxidase were densely and profusely distributed within the sarcoplasm. An interruption of staining was observed in the intercalated discs of the longitudinally sectioned fibers. *Phosphorylase* activity was observed also only in myofibers. The reaction for this enzyme was morphologically associated with cytoplasmic structures, the nuclei remaining unstained. The intensity of phosphorylase activity varied only slightly from fiber to fiber, and in general the heart muscle gave a moderate reaction for this enzyme. After *rapid transventricular ablation* the amount of the stainable labile fraction of *glycogen* was remarkably constant; it was distributed evenly in the individual fibers and only occasionally could a perinuclear aggregation of the granular deposits be observed. The cytoplasm of the muscle cells in sections digested with diastase to remove glycogen before staining was not colored, but the sarcolemma continued to be PAS positive.

Primary cardiomyopathies (Fig. 1). A decline in the activity of *monoamine oxidase* was usually seen in some parts of the myocardium about 3 to 5 hours after the injection of plasmocid or 24 to 48 hours after the administration of DHT. This spotty reduction in enzyme activity developed comparatively slowly; nevertheless, it obviously preceded the occurrence of any structural changes that could be detected by conventional staining techniques. During later stages of development most of the degenerating fibers were completely devoid of monoamine oxidase activity, but around such necrotic muscle fibers others were usually seen to show a partial loss of enzyme activity or a hyperactive state, as evidenced by an unusually intense reaction. Within the apparently unaffected parts of the myocardium the distribution and activity of monoamine oxidase was normal throughout the entire experiment.

Changes in the activity of myocardial *phosphorylase* also developed slowly, so that they often did not become obvious until 1 or 2 hours after the injection of plasmocid or 24 hours after the administration of DHT. During such early stages of involvement both a spotty decrease and an increase in enzyme activity occurred equally in the same hearts, and a complete loss of the reaction for phosphorylase did not prove to be a prenecrotic alteration; activity could still be detected in fibers already in various stages of disintegration. Alterations in the amount of *glycogen* deposits were seen as early as 30 minutes and 8 hours after the administration of plasmocid and DHT, respectively; here again, spotty decline (or sometimes even a total depletion) and significant increase were both observed in the same hearts. An analysis of serial sections revealed, furthermore, that the gradients for phosphorylase activity constantly followed the direction opposite from those for glycogen distribution. In fact, in some individual fibers there was a highly significant inverse relationship between these substances: in muscle cells completely devoid of glycogen the reaction for phosphorylase was elevated. During later stages of involvement, the fibers undergoing necrosis only occasionally contained glycogen granules which, when present, were few in number.

Finally, it is noted that the changes seen in the activities of monoamine oxidase and phosphorylase in hearts of rats kept on the potassium-deficient diet were similar to those seen in the other two primary cardiomyopathies, the only difference being that they developed even more slowly.

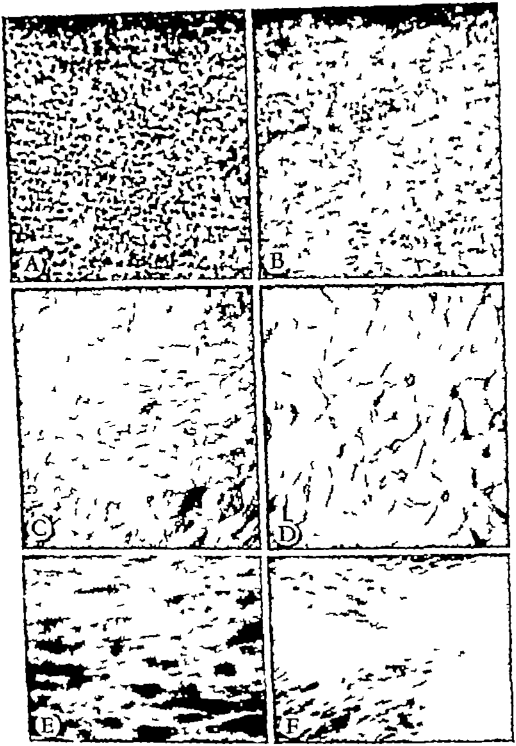


Fig. Early histochemical characteristics of the secondary ischemic type of necrotizing cardiomyopathy induced by methoxamine in the rat. *A* and *B*: Monoamine oxidase. The normal intensity of enzyme reaction (*A*) becomes significantly reduced (*B*) within the affected subendocardial region as early as 15 minutes after the administration of the vasoconstrictor substance. *C* and *D*: Glycogen. Partial (*C*) and total (*D*) loss of glycogen within subendocardial region at 15 and 20 minutes respectively. *E* and *F*: Phosphorylase. Spotty decrease (*E*) and a rather confluent loss (*F*) of enzyme activity at 15 and 20 minutes respectively.

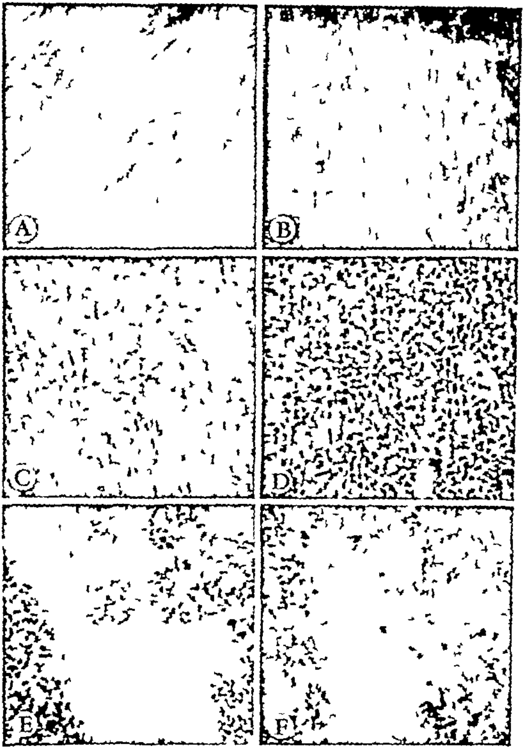


Fig. 3. Behavior of myocardial monoamine oxidase after coronary artery occlusion in the rat. Marked (*A*) and total (*B*) loss of enzyme activity within healthy areas, i.e., outside of the area supplied by the ligated trunk, at 40 and 70 minutes, respectively. *C*, Reappearance of enzyme activity at 28 hours. *D*, Normal reaction again at 76 hours within structurally normal myocardial areas. *E* and *F*, During late stages of involvement (i.e., at 96 hours) enzyme reaction is only totally absent within the infarcted regions; fibers surrounding such disintegrating foci always reveal some, although less than normal, enzyme activity.

the first obvious spotty alterations occurred around the seventh to tenth days whereas the presence of myocardial degeneration could not be diagnosed morphologically before the twelfth to sixteenth days However here the glycogen content of the myofibers gradually decreased until it completely disappeared from the entire myocardium much before the first necrotizing lesions could be evidenced

Secondary cardiomyopathies (*Figs 2-4*) In the coronary ligated hearts the behavior of *monoamine oxidase* proved to be quite different from that seen during the development of primary or metabolic cardiac lesions A significant reduction in or even a complete loss of the enzyme activity was already obvious within the area of the anticipated infarction as soon as 5 to 30 minutes after coronary artery ligature and somewhat later (i e 40 to 60 minutes) within the remaining unaffected parts of the myocardium But although in fibers in the ischemic zone there remained a constant absence of enzyme activity throughout the development of the massive infarct in the healthy myocardial fibers outside this territory



Fig 4 Behavior of myocardial phosphorylase during an advanced stage of development of the secondary cardiomyopathy induced by methoxamine *A* Histologic characteristics of ischemic necrosis at 7 hours *B* Loss of phosphorylase activity is restricted to the obviously degenerating region

the activity of monoamine oxidase returned from about the twenty-fourth to seventy-second hours. Similar phenomena were observed after the injection of vasopressor amines: within the affected regions a significant decline (gradually progressive until complete loss) in monoamine oxidase reaction was obvious as early as 15 to 40 minutes, whereas about 1 hour later the entire heart muscle became transiently devoid of enzymic activity. Nevertheless, here the prenecrotic foci showing losses in this enzyme were rather spotty and located mainly in the subendocardial and apical areas where the necrotic lesions are known to develop.

Reaction for *phosphorylase* could no longer be demonstrated within the areas of the anticipated infarction as early as 1 to 5 minutes after the onset of coronary occlusion. During later stages of involvement, this negative finding remained constant, independent of the duration of the anoxia and of the degree of degeneration. Furthermore, an equally speedy depletion of *glycogen* within the affected zone always paralleled the loss of enzyme activity. Outside the ischemic territory, the activity of phosphorylase and the amount of glycogen sometimes remained normal, but in most instances they became elevated. Similar parallel alterations of these two substances began as early as 15 to 30 minutes after the injection of vasopressor substances, and the foci showing phosphorylase and glycogen losses proved to be identical with those spotty territories in which the early decrease in monoamine oxidase reaction occurred. Muscle cells undergoing degeneration (myolysis or necrosis) rarely, if ever, showed any phosphorylase activity or glycogen content. However, in some fibers surrounding necrotizing foci, an increase in glycogen content could occasionally be detected, and such fluctuations in the amount of glycogen reserve were accompanied by variations in the reaction for phosphorylase always in the same direction.

Discussion

It is obvious from the comparative histochemical studies described in this paper that in the rat the behavior of the myocardial monoamine oxidase, phosphorylase, and stainable glycogen is determined by the type of necrotizing cardiomyopathy induced. It is stressed that—on the basis of earlier extensive studies[1,8,10,11]—the six different cardiomyopathies analyzed could be classified into two main groups: primary (nonocclusive or metabolic) lesions and secondary (occlusive or anoxic) lesions. The cardiomyopathies resulting from the injection of plasmocid, the administration of DHT, and the feeding of a potassium-deficient diet were grouped in the first category, since these potentially cardiotoxic influences are believed to act through direct metabolic effects rather than by interference with the normal coronary circulation. On the other hand, ligature of a coronary artery was used to elicit lesions of the classic occlusive type. In addition, the myocardial lesions produced by two highly potent synthetic amines (methoxamine and metaraminol), which possess sustained pressor and vasoconstrictor properties, were also considered to be secondary, since they are most probably ischemic infarctions in the pathogenesis of which coronary artery constriction and therefore anoxia plays a decisive role.[18,19] It is especially significant that, when such a categorization is applied, the apparent discrepancies in the present histochemical findings automatically disappear at once: the qualitative and quantitative changes seen in the reactions for monoamine oxidase, phosphorylase, and glycogen prove to be identical for the respective lesions, the basic difference in behavior arising from the type of lesion induced, i.e., primary or secondary.

The observation that monoamine oxidase—unlike other mitochondria-bound oxidative enzymes, such as succinic dehydrogenase and cytochrome oxidase[9,10]—is so sensitive to various potentially cardiotoxic influences, and especially to anoxia, may be of general significance, since, on the one hand, it is now well established that this enzyme is functionally related to the intracellular inactivation of catechol amines,[8,1] and, on the other hand, it has repeatedly been suggested that sympathomimetic amines may play a fundamental role in the pathogenesis of certain necrotizing cardiomyopathies.[7,17] Furthermore, the finding that during the develop

ment of ischemic infarction a transient inhibition of monoamine oxidase activity involving the entire heart muscle occurs may be taken to indicate that a compensatory mechanism comes into play in the affected heart which—through an inhibition of the enzyme—probably delays the degradation of the naturally present catecholamines and consequently promotes vasodilation Should this hypothesis turn out to be correct it would point up the existence of a defense mechanism within the heart that likely operates through the liberation of an endogenous monoamine oxidase inhibitor

Why a loss of phosphorylase activity is a prenecrotic alteration (i e enzymatic change that precedes histologically detectable structural abnormalities) only in cases of secondary or occlusive cardiomyopathies whereas it is rather an autolytic alteration (i e change that is accompanied by degeneration of the affected myocardial fibers) in primary or nonocclusive lesions is another basic question that awaits further clarification Similarly it would be difficult to explain on merely theoretical grounds why the alterations in phosphorylase activity and glycogen content run parallel after anoxic but not after direct metabolic damage inflicted on the myocardial fibers

Thus the present studies raised more questions than they answered nevertheless these comparative histochemical investigations suggest that (a) myocardial monoamine oxidase and phosphorylase are very sensitive to anoxia (b) in primary cardiomyopathies the early alterations in glycogen metabolism differ from those in secondary cardiomyopathies and (c) the histochemical demonstration of monoamine oxidase and phosphorylase in the heart muscle as well as comparative evaluation of the changes in reaction for phosphorylase and in variations in the amount of the stainable labile fraction of glycogen are of value in regard to the morphologic differential diagnosis between occlusive and nonocclusive cardiac lesions since they provide a basis for etiological considerations Whether these observations obtained on a large number of homogeneous animal materials are also applicable to human pathology remains to be established

Summary

Comparative histochemical and morphologic studies were performed during the development of three primary (nonocclusive or metabolic) and three secondary (occlusive or anoxic) necrotizing cardiomyopathies in the rat The primary types of lesion were induced by the injection of plasmocid the administration of dihydrotachysterol and the feeding of a potassium-deficient diet On the other hand the secondary types of cardiac damage were elicited by ligature of a coronary artery as well as by two synthetic amines methoxamine and metaraminol which possess sustained pressor and vasoconstrictor properties

It was observed that myocardial monoamine oxidase phosphorylase and the stainable labile fraction of glycogen behave differently during the development of primary and secondary cardiomyopathies and it is suggested that the histochemical techniques for these three substances are applicable for purposes of morphologic differential diagnosis since the changes are not only quantitatively but also qualitatively distinguishable and provide a basis for etiological considerations

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Case reports

Pericardial fat simulating cardiomegaly

*A. Everett James, Jr., M.D.**
Gainesville, Fla.
*Daniel J. Torrance, M.D.***
Baltimore, Md.

This case is presented as an example of excessive deposition of pericardial fat as a cause of apparent cardiomegaly. Although the pericardial fat pad is known to alter the contour of the cardiac silhouette, a search of the literature discloses no case of generalized cardiac enlargement due to pericardial fat.

Case report

H. S., a 37-year-old white man, presented with a history of shortness of breath, substernal discomfort, and paroxysms of coughing of 1 year's duration. The patient's weight had increased 60 pounds in the same period of time.

On physical examination the blood pressure was 140/90 mm. Hg. The pulse was 80 and regular. Examination of the heart revealed the point of maximum impulse to be 14 cm. to the left of the mid-sternal line in the fifth intercostal space. No murmur or friction rub was heard; the heart sounds were of normal intensity. There was no hepatomegaly, basilar rales, or ankle edema.

The chest x-ray film showed an enlarged cardiac silhouette with a double shadow at the junction of the heart and diaphragm on the left and right sides (Fig. 1). The impression at this time was that this might represent (1) pericarditis, (2) pericardial cyst, or (3) myocarditis.

The electrocardiogram was normal. Tomography of the heart showed a radiolucent border of several centimeters' thickness around a centrally situated normal-sized heart shadow (Fig. 2). This radiolucency represented an extensive accumulation of fat in the pericardial tissues. A mediastinal scan using I[131] labeled albumin was performed in order to outline the cardiac chambers for confirmation of this interpretation. The scanning image of the intracardiac pool was approximately the same size as the radiopaque heart shadow and within normal limits.

The final clinical impression was that the patient's symptoms were based on chronic bronchitis and sudden gain in weight. The suggestion was made that the increase in pericardial fat might have been related to the rapid increase in weight.

Comment

Anatomically, the mediastinal pleura lies in close apposition to the parietal peri



Fig. 1. Admission chest x-ray film shows enlarged cardiac silhouette.

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*Department of Medicine, The J. Hillis Miller Health Center, University of Florida, Gainesville, Fla. 32603.
**Associate Professor, Department of Radiology, The Johns Hopkins Hospital, Baltimore, Md.



Fig 2 Tomogram demonstrates the pericardial fat on the left and right sides of the centrally situated cardiac silhouette (which is of normal contour)

cardium A potential space exists between the two along the right and left cardiac borders This potential space is filled to a greater or lesser extent by loose connective tissues and a variable amount of fat The amount of fat which is present is dependent upon the general nutrition of the patient



Fig 3 Plain chest x ray film demonstrates radiolucent epicardial fat and its characteristic appearance in pericarditis

and is greater in obese individuals[3] The yellow fatty tissue in this area can be seen at postmortem examination or at the time of operation

The roentgenographic enlargement of the cardiac silhouette by pericardial fat was first described by Schwarz[4] in 1910 Many of his cases were confirmed at autopsy by the finding of large deposits of pericardial fat In Krautz and Pinner's report[5] there was autopsy confirmation of the increased pericardial fat seen in a chest film in which the cardiac silhouette was not grossly enlarged However tomography demonstrated a large radiolucent area outside the cardiac shadow

The differential diagnosis of an enlarged cardiac silhouette includes in addition to the deposition of fat around the pericardium pericardial effusion and cardiac dilatation Increased pericardial fat can be differentiated from pericarditis and cardiac dilatation by tomography Fat is the only body tissue that is radiolucent and will appear as a radiolucent area outlining the radiopaque heart muscle shadow In the case of pericarditis and dilatation the cardiac silhouette is homogeneous because fluid and heart muscle are of the same radiographic density[6]

Occasionally the subepicardial fat is

seen as a crescentic radiolucency within the otherwise homogeneous density of the pericardial effusion. As pointed out by Kremens[7] and Torrance[8] there is a radiopaque area outside the radiolucent area caused by the subepicardial fat (Fig. 3) thus differentiating pericardial effusion from the present case.

The triangular area at the apex of the heart caused by pericardial fat is commonly seen on chest x ray films. Although the etiology of its appearance is widely appreciated pericardial fat may be overlooked as a cause of apparent unexplained cardiomegaly.[9] It should be considered in an obese patient with apparent cardiomegaly when the clinical signs and symptoms are not so impressive as the enlarged cardiac silhouette.[10,11] The simplest and best technique for demonstrating the pericardial fat is tomography.

Summary

A case of pericardial fat that gave rise to an enlarged cardiac silhouette simulating cardiomegaly is presented. The virtual encasement of the heart by the large accumulation of pericardial fat led to difficulty in the differential diagnosis. The cardiomegaly was shown by tomography to be due to fat.

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Marfan's syndrome

Accelerated course in childhood associated with lesions of mitral valve and pulmonary artery

*Drummond H. Bowden, M.D.**
Blaise E. Favara, M.D.
James L. Donahoe, M.D.
St. Louis, Mo.

The predominant occurrence of the cardiovascular lesions of Marfan's syndrome in the left side of the heart and the aorta[1,2] suggests that localization of the abiotrophic changes of fibroclastic tissue may be determined in part by mechanical factors.

The importance of such factors is clearly demonstrated in this report of 2 cases of Marfan's syndrome in which the cardiovascular abnormalities resulted in death at an unusually early age.

Case reports

Case 1 (161/23). A 6-year-old white boy was admitted in September, 1956, for evaluation of a murmur which had been detected when he was 20 months old. He was asymptomatic but had developed slowly. There was no family history of skeletal abnormality.

On physical examination the child showed arachnodactyly, bilateral ectopic lentis, high arched palate, chest deformity, kyphoscoliosis, and hyperextensible joints. The cardiac rate was 100 per minute and the blood pressure was 100/72 mm. Hg. There was cardiomegaly to percussion. A Grade 3/6 pansystolic murmur at the apex radiated into the left axilla, and a localized apical mid-diastolic murmur was faintly audible. The pulmonic second sound was accentuated but not widely split.

The hemogram and urinalysis were normal. The electrocardiogram showed left ventricular dominance with inversion of T waves over the left ventricle. The chest x-ray film revealed moderate cardiomegaly and scoliosis. Catheterization of the right side of the right heart showed normal pressures and oxygen saturations and no shunt.

At 9 years of age, after repeated bouts of dyspnea, he was readmitted. The kyphoscoliosis and cardiomegaly were more pronounced, and cardiac failure was now present. The blood pressure at this time was 108/70 mm. Hg. The electrocardiogram (Fig. 1A) and chest x-ray films were unchanged. The findings of catheterization of the right side of the heart were normal and the boy was discharged.

Cardiac failure was progressive and he died in March, 1961, at the age of 10 years.

PATHOLOGY. Skeletal features typical of Marfan's syndrome were observed (Fig. 2). The heart (320 grams) exhibited pronounced hypertrophy of the left atrium and ventricle. The mitral valve leaflets were thickened and the chordae tendineae were unusually long (Fig. 3). The mitral ring (13.0 cm.) was much larger than usual at this age,[4] but in relation to the over-all size of the heart the amount of dilatation was not great. Endocardial thickening of the posterior wall of the dilated left atrium suggested significant functional mitral incompetence. The aortic valve (6.0 cm.) and the ascending aorta (8.0 cm.) were slightly dilated; the coronary vessels were normal. The tricuspid valve and the pulmonary outflow tract were unaffected, and the cardiac septa were intact. The cause of death was related to severe pulmonary edema and systemic venous congestion. *Microscopic examination* of the mitral valve showed abundant loose metachromatic staining tissue with few collagen fibers and

From the Departments of Pathology and Pediatrics, Saint Louis University School of Medicine, St. Louis, Mo.

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*Address: Department of Pathology, Saint Louis University School of Medicine, 1402 South Grand Blvd., St. Louis, Mo. 63104.

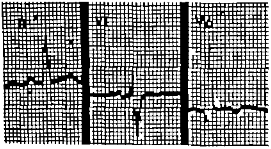


Fig 1A Case 1 Electrocardiogram shows left ventricular dominance and inverted T waves over the left ventricle The diphasic P waves over the right chest suggest enlargement of the left atrium

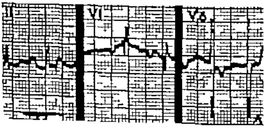


Fig 1B Case 2 Electrocardiogram shows right ventricular dominance and inverted T waves over the left ventricle The P waves are broad and notched there is a first-degree AV block with a P R interval of 0 19 second and a distinct rsR pattern in Lead V

no inflammatory cells The media of the ascending aorta showed focal fragmentation and swelling of elastic fibers with pronounced metachromasia The pulmonary artery and the major branches of the aorta did not show these changes

Case 2 (*A62/25*) A 3 month old white female infant was admitted in February 1962 because of cardiac failure The infant one of dizygotic twins weighed 2 600 grams at birth There was no family history of skeletal anomaly and the twin was normal

The child was moderately cyanotic pale and dyspneic Arachnodactyly dolichocephaly and a high arched palate were observed The cardiac rate was 160 per minute and a protodiastolic gallop rhythm was detected A systolic thrill was palpated at the cardiac apex where a loud mitral systolic murmur was heard to radiate widely The pulmonic second sound was accentuated and split during inspiration and expiration Rales were heard in both lung bases and the liver was enlarged

The hemogram and urinalysis were normal The electrocardiogram (Fig 1B) revealed right ventricular dominance a first-degree A V block and a distinct rsR pattern in Lead V Right ventricular enlargement was confirmed by the chest x ray film which also showed a prominent pulmonary segment and increased vascular markings in the lungs The findings supported the diagnosis of atrial septal defect

There was only temporary improvement with digitalis antibiotics and diuretics and the child died at 6 months of age

PATHOLOGY The heart (75 grams) showed hypertrophy of all chambers and the right atrium was greatly dilated The atrial septum showed a large (2 0 cm) simple secundum type of defect (Fig 4) Both leaflets of the mitral valve were patulous the chordae tendineae were loose and elongated and the mitral ring (7 5 cm) was dilated The tricuspid and aortic valves were normal and the ventricular septum was intact The root of the pulmonary



Fig 2 Case 1 Postmortem photograph shows the arachnodactyly and severe coliosis



Fig 3 Case 1 The mitral valve leaflets are thickened and the chordae are unusually long There is fibrous thickening of the atrial endocardium



Fig 4 Case 2 The mitral valve cusps are thickened and patulous A large septum primum defect is seen in the atrium

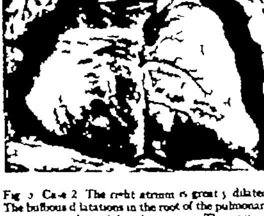


Fig 5 Case 2 The right atrium is greatly dilated The bulbous dilatations in the root of the pulmonary artery are indicated by the arrows The aorta is considerably smaller than the pulmonary artery

artery showed two bulbous anterior dilatations (Fig 5) and the wall was very thin The aorta coronary vessels and major arteries appeared to be normal

Severe pulmonary and systemic venous congestion were observed *Microscopic examination* showed lesions of the ascending aorta and mitral valve which resembled those described in Case 1 In addition however the pulmonary artery showed extensive disruption and metachromasia of the mural elastic tissue The small branches of the pulmonary artery (approximately 100μ in diameter) showed medial hypertrophy

Discussion

Deformity of the mitral valve is not uncommon in Marfan's syndrome[1, 4] It was the dominant cardiovascular abnormality in both of the cases presented and probably played a significant role in the early deaths

The absence of fibrous contracture readily distinguishes the mitral lesion of Marfan's syndrome from chronic rheumatic valvulitis The mechanics of mitral regurgitation in Marfan's syndrome are not known The patulous nature of the valves undoubtedly compromises their mobility and the elongated chordae may perhaps allow prolapse of the valve leaflets into the left atrium

Mitral incompetence was probably a major factor in the development of cardiac failure in the older child (Case 1) although the severe kyphoscoliosis may have contributed to the rapid cardiac decompensation

In the infant (Case 2) the left-to-right shunt through the atrial septal defect was augmented by regurgitation through the mitral valve Increased right ventricular output and resultant pulmonary hypertension may be inferred from the hypertrophic changes which were observed in the precapillary vessels of the lung The hemodynamic disturbance may also explain the unusual involvement of the main pulmonary trunk and the relative sparing of the ascending aorta

It seems therefore that although the abiotrophic changes of Marfan's syndrome are genetically induced[1, 4] hemodynamic factors determine the site and severity of the vascular lesions Thus in Case 1 the aorta which was subjected to normal systemic pressure was dilated In contrast the infant with pulmonary hypertension showed aneurysmal dilatation of the pulmonary artery and the aorta was less severely involved

Summary

Two cases of Marfan's syndrome are described The rapid development of cardiac failure which resulted in the early death of these children was probably in

fluenced by severe involvement of the mitral valve in both instances One patient showed the classic features of the syndrome with dilatation of the ascending aorta the other had a large defect of the atrial septum and aneurysmal dilatation of the pulmonary artery

The localization and progression of the cardiovascular changes in Marfan s syndrome appear to be largely dependent on hemodynamic factors

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Fig. 4. Case 2. The mitral valve cusps are thickened and patulous. A large septum secundum defect is seen in the atrium.



Fig. 5. Case 2. The right atrium is greatly dilated. The bulbous dilatations in the root of the pulmonary artery are indicated by the arrow. The aorta is considerably smaller than the pulmonary artery.

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It seems, therefore, that although the abiotrophic changes of Marfan's syndrome are genetically induced,[1, 8] hemodynamic factors determine the site and severity of the vascular lesions. Thus, in Case 1 the aorta, which was subjected to normal systemic pressure, was dilated. In contrast, the infant with pulmonary hypertension showed aneurysmal dilatation of the pulmonary artery, and the aorta was less severely involved.

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Some unanswered questions concerning enlargement and failure of the heart

Grady Reddick Memorial Lecture

*Tinsley R. Harrison, M.D.**
Birmingham, Ala.

My first meeting with Grady Reddick occurred about 25 years ago at a medical convention in Dallas. An unusual and bizarre case history was presented for discussion at a clinical pathologic conference. I, like the several other visitors, went completely astray in my reasoning about the diagnosis. The pathologist was the late Dr. George Caldwell. He was too hospitable to twist the barb in the flesh of the guests, but the Scotch twinkle in his eye indicated his pride in finding that the local clinical representative, Dr. Reddick, was the only one to arrive at the correct answer.

Some years later, during the Second World War and while Dr. Reddick was on active duty in the Navy, I, having moved to Dallas, succeeded him as Physician-in-Chief at the old Parkland Hospital. (What a difference from the present magnificent institution which now bears the same name!) Upon his return from service, I suggested that he reassume his former position. His reply was characteristic. After thanking me for the offer, he made it abundantly clear that the Chairman of the Department of Medicine and the Physician-in-Chief of the Parkland Hospital must of necessity be the same individual and that he had no wish to be either, much less both. However, he did desire to continue teaching and would be happy to accept any educational assignments which the departmental chairman, myself, might suggest. To my previous admiration for his clinical acumen was now added appreciation for his unselfishness and gratitude for the manner in which he overcame my embarrassment at having taken the position of one who was absent for the purpose of fighting my battles. He thus absolved me from my David-Uriah complex. Parenthetically, one may remark that the analogy of Parkland—or any other hospital—with Bathsheba is perhaps not too farfetched. Such unpredictable, contrary, and fascinating institutions as hospitals must belong to the feminine gender.

During the several subsequent years of our association, the sentiments toward Dr. Reddick as mentioned above ripened into a warm friendship. I never knew him to speak an insincere word or to perform a selfish act. He was not only an astute bedside observer and an inspiring teacher but also a devoted student of medicine

From the Department of Medicine, Medical College of Alabama, Birmingham, Ala.
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*Address: Department of Medicine, University of Alabama Medical Center, 1919 Seventh Avenue South, Birmingham 3, Ala.

The subject selected for this memorial lecture is one which I hope and believe would have interested him

The unanswered questions which are to be discussed have arisen mainly from the work of my colleagues during the past 10 years and particularly from the studies of Dr E E Eddleman Dr Lloyd Hefner and Dr T Joseph Reeves It is our wish that not only our own group but also other investigators will attempt to find the answers

The scientific method involves two essential steps One must first formulate a problem i e ask a question Then one attempts to arrive at a solution or to answer the question It so happens that the research tool which has been of particular interest to me during the past decade is especially useful for the first purpose although of limited value for the second A brief explanation will clarify our subsequent discussion

The movements of the cardiac apex in relation to those of the surrounding precordial areas have long been studied In recent years the correlation of these apex cardiograms with other circulatory phenomena such as the electrocardiogram the heart sounds and the carotid pulse have yielded useful information concerning such matters as the time of onset of cardiac filling[1] and the pathophysiology of ischemic heart disease Our own interest has been centered on *absolute* precordial movements in relation to a fixed external point Tracings of this type which we call kinetocardiograms (KCGs) are surprisingly similar in all healthy young persons when recorded from corresponding anatomic points but in a given person display striking variations from one area to another (Fig 1)

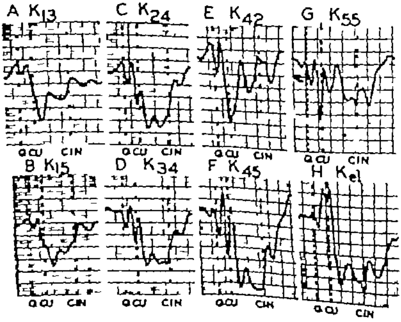


Fig 1 L B 23 year-old woman with normal heart Time lines 0 02 sec Each trace displays one cardiac cycle beginning and ending at P Recording sensitivity 2.5 as great in E to H as in A to D K (A) and K15 (B) were taken in the right parasternal line in the third and fifth intercostal spaces K24 (C) K (D) K (F) and K (G) were taken from V, V V and V points respectively K (E) was taken from the second intercostal space in the V line K (H) was taken from the left epigastrium The records in different intercostal spaces in the same vertical line display slight (A B) to marked (E F) differences Traces from the V (C) V (D) V (F) and V (G) positions also exhibit slight (C D and F) to marked (F and G) differences Configurations from the right precordial area (A B) are different from those from the left precordial region (C D F)

In these respects they are analogous to precordial electrocardiograms.

Each kinetocardiographic record displays 8 or more deflections. Since we usually record from 25 different areas (or "leads"), the records from a single subject display more than 200 variables, each of which needs to be studied in relation to the simultaneously recorded reference traces. As a routine, the electrocardiogram and the carotid pulse are used, but in some circumstances heart sounds or intracardiac pressures have been employed. Thus one obtains a large mass of information related to cardiac activity in the records from a single subject. However, this information is indirect and imprecise. It tells us about movement of the chest wall but not directly about pressure, flow, or cardiac work. One cannot even be certain that these motions represent exact reflections of the movement of the underlying heart. The physical properties of the intervening structures may cause them to differentiate or otherwise modify the forces transmitted to them by the alterations in volume, shape, or position of the underlying chambers.

The KCG is sometimes of clinical value in terms of the recognition of right or left

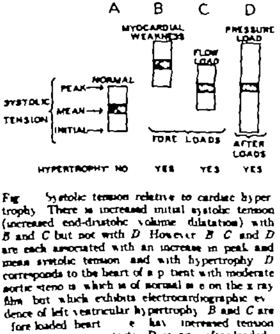


Fig. Systolic tension relative to cardiac hypertrophy. There is increased initial systolic tension (increased end-diastolic volume, dilatation) with *B* and *C* but not with *D*. However, *B*, *C*, and *D* are each associated with an increase in peak and mean systolic tension and with hypertrophy. *D* corresponds to the heart of a patient with moderate aortic stenosis which is of normal size on the x-ray film but which exhibits electrocardiographic evidence of left ventricular hypertrophy. *B* and *C* are fore-loaded hearts, i.e., have increased tension before contraction starts. *D* is an after-loaded heart and is subjected to increased tension only after contraction begins.

ventricular hypertrophy or of ischemic heart disease.[4-6] But its greatest practical usefulness is in teaching us to palpate and thereby in augmenting our bedside acumen.[4] Because of the mass of information provided, the method is especially useful for asking questions; since such information is indirect and imprecise, the final answers must be sought by *other techniques*. With these limitations clearly in mind, we may now consider these questions.

Mechanisms and effects of cardiac enlargement

A sharp distinction should be drawn between increase in the size of the cardiac x-ray shadow, which may be due to pericardial fluid or to an apical fat pad, and an actual increase in size (volume or weight) of the heart itself. Here we are concerned only with the latter.

Causes of dilatation. One of the important conceptual advances of the past 15 years has been the clear demonstration that the simple relationship existing in the heart-lung preparation between stroke work, myocardial fitness, and ventricular volume is altered in the intact animal by a variety of regulatory mechanisms which affect peripheral resistance, venous return, and myocardial responsiveness. To name only a few of the many investigators who have contributed to this important modification of older concepts, we may cite Stead and Warren,[7] Rushmer,[8] Sarnoff,[9] Reeves,[10] Hefner,[11] and their colleagues. Nevertheless, numerous observations on man[12] have confirmed the principles formulated by Otto Frank and by Ernest H. Starling. Thus, cardiac dilatation in man is probably always associated either with increased load or with myocardial disease and is intimately related to a rise in the ratio of load to strength. The absence of dilatation in patients with well-tolerated aortic stenosis is probably due to a parallel increase in load and strength because of compensatory hypertrophy.

There is ample evidence that hypertrophy is also related *not necessarily to either load or strength but to the ratio of one to the other*. Thus, prolonged and persistent elevation of pressure (hypertension, aortic stenosis) or flow (severe anemia, arteriovenous fistula) leads to hypertrophy

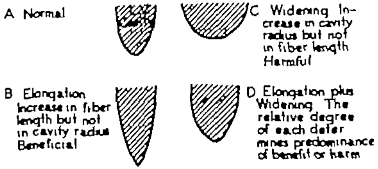


Fig. 3 Hypothetical relationship between change in shape and the beneficial or harmful effect of dilatation. This is an oversimplified diagram based on the assumption which is only partially true that all fibers are oriented in the base-to-apex direction. It is unlikely that the conditions illustrated in *B* and *C* ever occur in patients with dilated ventricles who always have a combination of some increase in length and in breadth of the ventricular cavity. But the relative degree of each should determine whether the beneficial Starling effect (increased fiber length) or the harmful Laplace effect (increased radius) predominates.

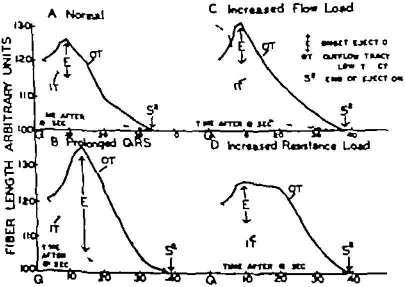


Fig. 4 Probable relationship of hemodynamic alterations to cardiac hypertrophy. *A* During the isovolumic interval the late-excited outflow tract is passively stretched because of shortening of the early-excited inflow tract. This phenomenon is markedly exaggerated in *B* because of the longer interval before the outflow area begins to shorten. The theoretical result should be increased mean systolic tension and hypertrophy of the outflow tract only. *C* It is assumed that the thin walled inflow tract (apex) is disproportionately stretched by the augmented *filling*. The stronger contraction of this area during the isovolumic period will lead to increased initial stretch of the outflow tract. The net result should be balanced hypertrophy of both areas. *D* Conditions are normal during the isovolumic interval. During early ejection the resistance to shortening affects the area of late excitation (outflow tract) which is only beginning to contract more than the *earlier-excited inflow tract* which has now reached its peak of contraction. The net effect—moderate and marked increase in tension in the inflow and outflow tracts respectively—should be disproportionate hypertrophy of the latter area. Pending experimental testing these concepts are purely hypothetical.

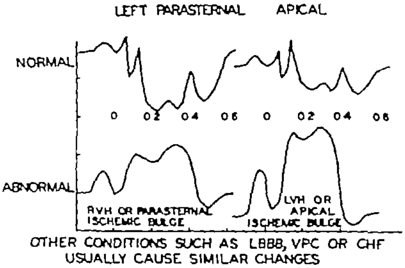


Fig. 5. Each precordial trace begins and ends with the onset of the R wave of the ECG and depicts one cardiac cycle. The period from the start of ventricular excitation (zero) to the end of ejection is approximately 0.4 sec. Upstrokes and downstrokes signify outward and inward motions, respectively. The normal record (*above*) exhibits slight outward and larger inward motion during isovolumic contraction (alterations in shape and/or position), a somewhat larger abrupt outward deflection (recoil) as ejection starts, and predominant inward movement during the remainder of systole. The abnormal traces (*below*) display exaggerated and prolonged paradoxical outward motion throughout systole, there being only a small inward deflection during the early part of ejection. The term asynergy (*see text*) is used to designate such a state of wasted work. Hypertrophy and ischemia are associated with the most striking degrees of asynergy. Less pronounced but qualitatively similar changes are commonly seen in patients with abnormal excitation or congestive failure (Figs. 10, 11, and 12).

As was reported by Davis and Blumgart[13] and by van Peenen and Gerstl,[14] pronounced hypertrophy also occurs in patients with coronary disease who lack both clinical and *postmortem* evidence of increased cardiac work.

If both dilatation and hypertrophy are related to elevation of the ratio of load to strength, the natural assumption would be that dilatation, which is the immediate response, always precedes and in some way causes hypertrophy, which appears to be a delayed response to an increase in the ratio. But there is at least suggestive evidence that this assumption is not always valid. Thus the x-ray film indicates that patients with moderate aortic stenosis often have normal sized hearts, i.e., no dilatation, despite undoubted electrocardiographic signs of left ventricular hypertrophy.

What then is the essential stimulus to hypertrophy? The Laplace equation, Tension = Pressure × Radius, may supply the answer. The above-mentioned considerations indicate that, although an increase in *pressure or in radius (volume) may precede* hypertrophy, neither does so invariably. Can an increase in tension be the cause, as was suggested by Bohnenkamp[16] and by Linzbach[17]?

A distinction must be drawn between initial systolic (end-diastolic) and mean systolic tension. If the end-diastolic pressure remains constant, the initial tension in the ventricular cavity will be elevated by any *condition which increases its end-diastolic radius*. If, during the ensuing systole, the pressure developed and the volume of blood expelled remained constant, the mean systolic tension would be increased. These conditions (Fig. 2 *B* and *C*), which illustrate the "fore-loaded heart" (Wiggers), can explain hypertrophy as a consequence of dilatation produced either by myocardial weakness (diminished sys-

tolic emptying) or elevated flow loads (augmented diastolic filling) But increased initial tension will not account for hyper trophy in the undilated after loaded heart of a patient with aortic stenosis and a normal end diastolic pressure

The situation of a vigorous small heart which is subjected to a systolic pressure load but which is still able to eject nor mally is illustrated in Fig 2 *D* Although the initial systolic tension is normal the mean systolic tension is elevated because of the elevation of pressure

These considerations lead to a tentative conclusion *The probable stimulus to hyper trophy is mean systolic tension* Although this hypothesis is in keeping with the known facts it is based on *a priori* reasoning from indirect evidence and needs to be tested by direct experiment The possibility that a slight but undetectable amount of dilatation precedes hypertrophy and then disappears as myocardial strength in creases cannot be excluded with certainty

Clinical medicine teaches us that there is a close correlation between cardiac size and cardiac failure Why should this be true when it seems obvious that both dilatation and hypertrophy are initially compensatory responses to an increase in the load to strength ratio?

The effects of dilatation The report of Burch and his colleagues[11] dealing with this subject represents one of the more important recent contributions to cardio-vascular physiology They contrasted the well known advantage of dilatation i e increased fiber length with the more vigor ous contraction as previously emphasized by the studies of the Starling group with the disadvantage i e the necessity for increased mural tension in order to pro duce a given intracavitary pressure They indicated that the net result of increased ventricular volume (dilatation) will thus depend on the relative predominance of these two effects The same concept had been advanced by Roy and Adami[12] more

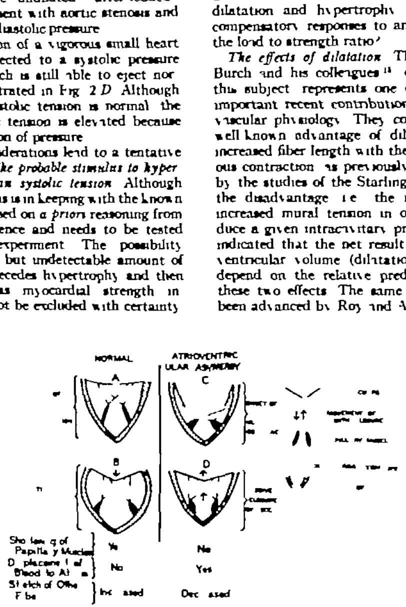


Fig 4 Effect of type of valve closure on ventricular function *A* The immedi ately preceding atrial relaxation has reduced atrial pressure and caused the mitral cusps to ascend When ventricular systole begins the now stretched papillary muscles contract vigorously and produce closure by descent without escape of blood into the atrium (*B*) The resulting change in shape of the cavity causes increased stretch and stronger contraction of the other ventricular fibers *C* Either an absence of coordinated atrial function (fibrillation) or an ab- normal interval between contraction of the two chambers permits the atrial pressure to exceed the ventricular Hence the cusps are widely open and the papillary muscles are not stretched as ventricular systole begins The pas sive ascent of the cusps (*D*) results in displacement of blood into the atrium with diminished stretch and less vigorous ventricular contraction The normal synergistic teamwork between atrium and ventricle has been disrupted

Table I. Types of ventricular work

Remarks	Essential	Wasted	Remarks
Ventricular efficiency closely related to ratio Essential work / Wasted work	1. Isovolumic, i.e., that required to raise pressure to aortic level	3. Positional, i.e., moving the cardiac muscle mass	Positional work probably a small fraction in all patients
	2. Ejection, i.e., that involved in expelling blood	4. Shape, i.e., that expended by some fiber in stretching others	Normal: Significant shape work only during isovolumic contraction
			Disease: Increase in shape work throughout systole

Interventions that may [illegible] the [illegible] of ventricular efficiency and [illegible] by increase $\frac{\text{Wasted work}}{\text{Essential work}}$ and $\frac{\text{Shape work}}{\text{Ejection work}}$

than one half century earlier: the strain upon the walls of a sphere or spheroid increases with its circumference and therefore the resistance to contraction of the heart is increased whenever it becomes dilated. But this application of the Laplace principle to the heart was apparently overlooked by most investigators until re-emphasized by the Tulane group.

In Fig. 3 are illustrated certain purely theoretical concepts. The evidence of the bedside and of the postmortem table tell us that the conditions illustrated in *B* and *C* of Fig. 3 probably never occur in patients who display combinations of elongation and widening, as in *D*. If we assume that such is the case, we then arrive at an important principle: *Whether dilatation is mainly beneficial or harmful will depend on the type of change in shape*. When, because of elongation, fiber stretch predominates over increased cavity size, the net effect will be beneficial, but when, because of widening, volume is increased more than stretch, the effect will be harmful.

Some possible effects of hypertrophy. Some effects of hypertrophy are illustrated in Fig. 4. There is ample evidence from the electrocardiogram and from the postmortem table that the conditions illustrated, i.e., prolongation of ventricular excitation and disproportionate thickening of the base as compared to the apex, frequently occur when hypertrophy is marked. Each will presumably tend to cause a greater increment in the vigor of shortening of the late-contracting areas as compared to the early contracting areas. It is probable, although not established beyond question, that this disproportion is responsible for the pronounced and prolonged paradoxical outward motion so commonly observed in persons with right or left ventricular hypertrophy (Fig. 5). That such a heart wastes energy can be seen by comparing these exaggerated motions with the normal abrupt and brief recoil motion as ejection begins (Fig. 1 *F*). The work expended by the remaining portions of the ventricular mass in protruding these areas, despite their own contraction, is obviously wasted in so far as expelling blood is concerned. A condition of poor teamwork, or asynergy, exists between the different portions of the same ventricle. Certain additional aspects of cardiac asynergism may now be considered.

Heart failure and asynergy

During the past 20 years measurements of pressure and flow made possible by cardiac catheterization have added immeasurably to our exact knowledge of what the human heart does and fails to do. (That some of the finest work in this field has been conducted here in Dallas by Carleton Chapman and his associates is a source of pride to us all.) We may now address ourselves to a related problem: *How* and *why* does the performance of the failing heart become inefficient? This

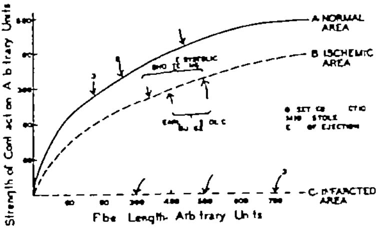


Fig 7 Hypothetical Starling curves of different portions of the left ventricle in a patient with ischemic heart disease *A* and *B* During early systole (*1* to *2*) the healthy muscle shortens not only because of ejection but also because of displacement of blood into the ischemic bulging area During late systole the latter region is able because of greater stretch to shorten more than does the normal area which has previously undergone marked shortening Thus the energy expended by the normal muscle in stretching the ischemic but still viable region is not entirely wasted *A* and *C* The infarcted region has a flat Starling curve no matter how much it is stretched it cannot contract Thus the energy expended in stretching it and the loss of contractile power in the healthy muscle because of the change in shape is completely wasted A patient with a previous infarct who also has angina would be expected to have all three curves and also numerous intermediate ones depending on the degree of ischemia in the different portions of the left ventricle

Table II *Some probable mechanisms of cardiac asynergy*

Atrioventricular

- Abnormal P R interval
- Atrial fibrillation

↓ Abnormal A V closure
↓ Displacement of blood from ventricle
↓ Diminished stretch of ventricle
↓ Weaker contraction

Intraventricular

- Disproportionate hypertrophy
- Ventricular premature beats
- Ischemia
- Prolonged QRS
- Extreme tachycardia

↓ Different Starling curves for different portions of same ventricle
↓ Decrease in ratios

Both lead to:

Less complete ventricular emptying
↓ Elevation of ventricular diastolic pressure
↓ Clinical manifestations of congestive heart failure

and

Essential work / Wasted work

and

Ejection work / Shape work

leads to an analysis of some of the various respects in which its own teamwork may be defective.

Atrioventricular asynergism. There is good evidence[16] that under normal conditions the atrioventricular cusps ascend just before ventricular contraction starts. That this is due to atrial relaxation with transient reversal of the atrioventricular pressure gradient is strongly indicated by the studies of Skinner, Wallace and Mitchell.[17,18] Under rigidly controlled conditions they found in dogs that not only during auricular fibrillation with artificial regular ventricular rhythm but also when the P-R interval was abnormally long or abnormally short, the stroke volume of the left ventricle was diminished. The likely explanation is illustrated in Fig. 6. When, as probably occurs with a normal P-R interval, the immediately preceding atrial relaxation produces semiclosure of the atrioventricular cusps, the stretched papillary muscles complete the process by relatively vigorous contraction with *descent of the cusps*. There is no loss of blood into the atrium, and the change in shape causes some additional stretch of the ventricular fibers (Fig. 6 *A* and *B*). Disorders cited above which disturb the normal temporal relationship of ventricular to auricular contraction probably produce *closure by ascent* (Fig. 6 *C* and *D*). This causes feeble papillary contraction, displacement of blood into the atrium, and reduction in the size of the ventricular cavity, with decrease in fiber stretch.

It is not likely that atrioventricular asynergy alone can lead to heart failure. But when other deleterious factors coexist (see later discussion), this harmful influence may be expected to cause further impairment of ventricular function.

Interventricular asynergism. That there is some functional interrelationship between the two ventricles was suggested by the experiments of Starr and associates.[19] They found that dogs survived despite destruction of the entire free wall of the right ventricle. Presumably, the left chamber and/or the interventricular septum were able in *some manner* to facilitate ejection by the right. It is probable that conditions such as ventricular premature beats and bundle branch block which lead to earlier contraction of one ventricle than of the other impair interventricular synergism. Abnormal movements of the interventricular septum due to excessively strong (or weak) contraction of one ventricle as compared to the other might have a similar effect. Finney[19b] has studied the comparative effects of stimulation of various subendocardial sites on the left ventricular function (rate of rise in pressure and rate of rise in tension) of dogs. As compared with the normal supraventricular excitation, progressive impairment occurred when the apex of the left ventricle, the base of the left ventricle, and the right ventricle were stimulated. His observations supply support to the concept of interventricular asynergy and also suggest that any type of abnormal *asynchrony tends to produce asynergy*.

Intraventricular asynergy. The most extreme form of intraventricular asynergy is ventricular fibrillation, in which all coordination of contraction is lost and all energy is wasted. The lesser degrees may be considered to be disorders in which the different portions of the same ventricle have different Starling curves (Fig. 7). Ischemia and hypertrophy are the most important but not the only causes of the disturbed teamwork. Extreme supraventricular tachycardia is another cause. There is evidence (Fig. 8) that in this state some fibers are still incompletely relaxed when others are starting to contract. A portion of the energy derived from the latter is then expended in stretching the former.

The heart expends energy in several ways. In the process of conversion of chemical energy to mechanical work, a certain fraction is lost as heat and friction. Upon excitation, the ventricular myocardium can either produce tension or shorten or do both. These activities are in turn reflected in either wasted or essential work. The latter includes both the isovolumic fraction, i.e., that involved in raising pressure, and the subsequent ejection fraction (Table I). The wasted work is that which causes alterations in the shape or position of the cardiac chambers. Except for the brief recoil movements as ejection begins, the changes in position during the cardiac cycle are normally slight. *It is probable, therefore, that the*

ratio of ejection work to shape work is a crude guide to the ratio of essential work to wasted work which in turn is a rough index of the effectiveness of the heartbeat The KCG although unable to provide quantitative data concerning changes in



Fig 8 These curves represent tension (*T*) and the first derivative (*dT*) of tension as recorded by a strain gauge arch from the left ventricular wall of a dog with spontaneous atrial fibrillation The solid vertical time lines indicate 0 04 sec The dotted vertical lines designate the onset of QRS in the simultaneously recorded ECG which is not shown The solid horizontal base line depicts zero tension or complete relaxation The tension trace reaches the zero base line only during the longer diastolic intervals of complexes *2 5 8* and *11* In each of the other beats contraction starts (upstroke of tension curve) before relaxation has been completed Both the peak tension achieved (height of T) and the rate of development of tension (height of dT) are much greater in those beats (*3 6 9*) which follow complete relaxation

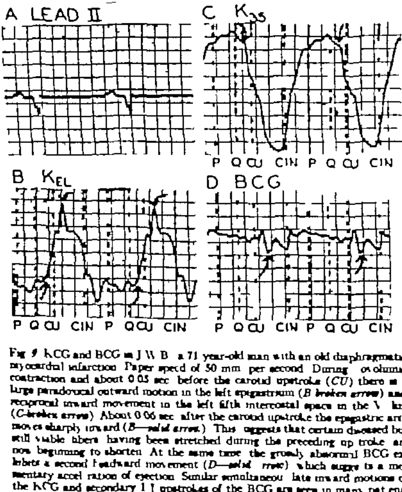


Fig 9 KCG and BCG in J W B a 71 year-old man with an old diaphragmatic myocardial infarction Paper speed of 50 mm per second During isovolumic contraction and about 0 05 sec before the carotid upstroke (*CU*) there is a large paradoxical outward motion in the left epigastrium (*B broken arrow*) and reciprocal inward movement in the left fifth intercostal space in the V line (*C broken arrow*) About 0 06 sec after the carotid upstroke the epigastric area moves sharply inward (*B—solid arrow*) This suggests that certain diseased but still viable fibers having been stretched during the preceding upstroke are now beginning to shorten At the same time the grossly abnormal BCG exhibits a second headward movement (*D—solid arrow*) which suggests a momentary acceleration of ejection Similar simultaneous late inward motions of the KCG and secondary I J upstrokes of the BCG are seen in many patients with ischemic heart disease

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have exhibited this phenomenon at one or more precordial areas during the attacks[1,4] the abnormality diminishing or disappearing as the pain subsided

The majority of patients with ventricular premature beats (Fig 10) or left bundle branch block (Fig 11) including most of those who present no other evidence of structural heart disease exhibit paradoxical motion[4] *This is less constant in persons* with right bundle branch block

Because of the necessity for suspended respiration while precordial tracings are being made it is difficult to secure satisfactory records in severely dyspneic patients All subjects with biventricular congestive failure who have thus far been studied have displayed paradoxical movement at one or more areas[10] The abnormality usually lessens but rarely disappears completely when improvement occurs (Fig 12) This would suggest that the paradoxical movements are partially related to heart failure itself and partly to such commonly associated factors as hypertrophy arrhythmias prolonged intraventricular conduction etc

The general concept of ventricular asynergy is shown in an *oversimplified* and diagrammatic form in Fig 13

The sequence illustrated in Table II represents a partial summary of some as yet hypothetical answers to some of the questions which have been discussed The table is incomplete Thus because we have little information about it interventricular asynergy has been omitted despite its probable importance in a variety of disorders Similarly no mention is made of atrial premature beats the Wolff Parkinson White disorder or nonischemic myocardial disease Ventricular tachycardia is also omitted as is ventricular fibrillation which is the most extreme form of cardiac asynergy with zero ratios for ejection work to shape work and essential work to wasted work

The purpose of Table II is to illustrate the principle that the summation of a variety of noxious influences each one of which could be tolerated if existing alone may cause such a high degree of disorganization of the normal cardiac synergy that heart failure ensues

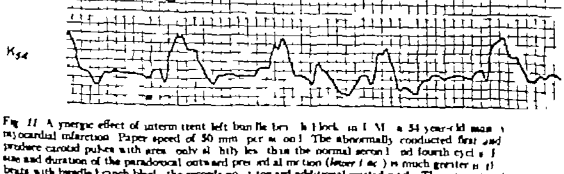


Fig 11 Asynergic effect of intermittent left bundle branch block in I M a 54 year old man with myocardial infarction Paper speed of 50 mm per second The abnormally conducted first and produce carotid pulses with areas only slightly less than the normal second and fourth cycle size and duration of the paradoxical outward precordial motion (*lower trace*) is much greater in beats with bundle branch block the records point toward additional wasted work The *premature* beat (*third complex*) produces only a small precordial movement But since there is no carotid pulse done by the left ventricle totally wasted The trace illustrates two different varieties of asynchrony as well as a third type the paradoxical outward movement of the normal disease per se

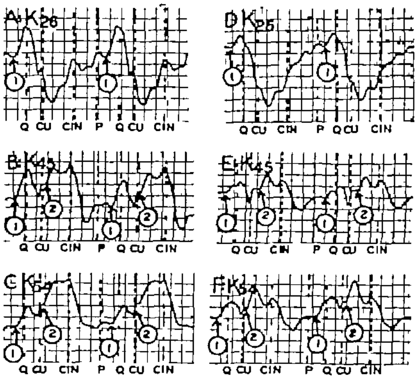


Fig. *12* Effect of digitalis on cardiac asynergy in J. F., a 65-year-old man with an old myocardial infarction and mild congestive failure. Paper speed *of 50 mm. per second. Each trace includes two complexes beginning and ending* with the P wave of the ECG. During the 5 day interval between *A, B, C* and *D, E, F* the patient was digitalized with improvement in dyspnea, circulation time, and vital capacity. The atrial motions (*first arrow*) were diminished after the drug. This is indirect evidence of decreased atrial (and ventricular) diastolic pressure.[illegible] The paradoxical outward systolic motions (*second arrow*) were of smaller magnitude after digitalization.

The comparison of the heart to a football team is admittedly farfetched but may be useful in illustrating these concepts. One may think of the heart which fails because of a mechanical overload as a poorly coordinated team in which each individual player is large and powerful (hypertrophy). An occasional offside penalty (premature beat) does not seriously impair its effectiveness. Incomplete forward passes (beats which expel no blood) become serious when too numerous. But when we add to these handicaps a situation in which the line fails to charge (atrial fibrillation), the different players start moving at widely different times (prolonged excitation) and the blocking backs move in one direction while the ball carrier travels oppositely (intraventricular asynergy), we are obviously observing an ineffective team (heart failure). Certain loss of the game (death) is inevitable either when all players move in uncoordinated directions (ventricular fibrillation) or no players move in response to signals (standstill) or when no signals are called (cessation of electrical activity).

Our final and most important question is as follows. Granting that these abnormal systolic alterations in shape and possibly in position represent wasted work, how do we know that the *degree of waste* is sufficient to constitute a grave handicap to the heart? The studies of Tennant and Wiggers[illegible] and of Murray[illegible] on the hemodynamic effects of ischemic ventricular bulges in dogs pointed toward a significant amount of functional impairment. The more recent comparison by Tyson and associates[illegible] of expansile with nonexpansile prostheses inserted into the apical region of dogs indicated that the former but not the latter caused reductions of as much as

30 per cent in left ventricular function. Presumably the same principle applies in the human heart. But this has not been demonstrated and until such direct proof is available the concepts which have been discussed must be regarded as hypotheses which although perhaps interesting and logical remain to be established.

Summary

Certain observations and certain related but as yet incompletely answered questions may now be listed.

1. Hypertrophy may exist in the absence of clear evidence of coexisting or

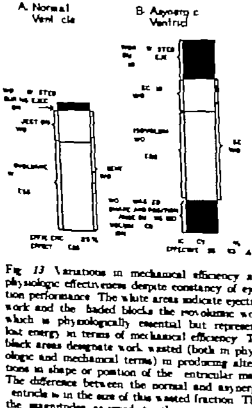


Fig. 13. Variations in mechanical efficiency and physiologic effectiveness despite constancy of ejection performance. The white areas indicate ejection work and the shaded blocks the isovolumic work which is physiologically essential but represents lost energy in terms of mechanical efficiency. The black areas designate work wasted (both in physiologic and mechanical terms) in producing alterations in shape or position of the ventricular mass. The difference between the normal and asynergic ventricle is in the size of this wasted fraction. That the magnitudes assigned to these various types of work are arbitrary does not invalidate the concepts involved. The diagram is based on several assumptions: (1) that all of the chemical energy is converted into mechanical work, the dissipated heat being negligible; (2) that the ejection work (pressure X flow) is the same for the two ventricles; (3) that the ratio *ejection work to total work* is an accurate guide to the mechanical efficiency; and (4) that the ratio *essential work to total work* is a reliable index of physiologic effectiveness. The obvious quantitative dubiousness of these assumptions does not alter the principle, which is that marked physical and physiologic impairment may occur despite normal performance of ejection work.

pre-existing dilatation. Does this mean (a) that undetected dilatation has necessarily been previously present or (b) that dilatation is not an invariable antecedent to hypertrophy which is caused rather by an increase in the mean systolic tension?

2. Dilatation may be either beneficial or harmful. Is it possible that the net effect depends on the change in shape, i.e., on the relative predominance of increased stretch (beneficial) versus increased radius (harmful)?

3. *Atrioventricular asynergy.* Distortion of the normal temporal relationship between atrial and ventricular contraction reduces the effectiveness of the latter. Is this due to an abnormal type of valve closure, i.e., by ascent with displacement of blood into the atrium as compared to normal closure by descent?

4. A decline in the ratio of essential work to wasted work necessarily implies a decrease in ventricular effectiveness. To what extent is this quotient comparable to the ratio of ejection work to shape work during systole?

5. *Intraventricular asynergy.* There is ample evidence that a variety of conditions, including among others hypertrophy, ischemia, extreme tachycardia, prolongation of ventricular excitation, and abnormal pathways of excitation, may lead to a marked increase in shape (and or positional) work as shown by exaggerated outward systolic motion. This signifies disturbed teamwork (asynergy) between the different parts of a single ventricle. Is the quantitative significance of this sufficient to be a highly important factor in the production of heart failure?

6. The extreme phase of cardiac asynergy is ventricular fibrillation, in which the chamber has a flat Starling curve. Is it permissible to look on lesser degrees of ventricular asynergy as conditions in which the different portions of the same chamber have different Starling curves?

In closing this discussion two points should be emphasized. First, the concepts herein mentioned have stemmed from the work of a group of investigators and not solely from that of myself. Second, these ideas, although derived from past research, have little merit except as avenues of ap

proach to future studies. Although they appear to be compatible with presently known facts, their validity can only be established by the accumulation of many new facts. The efforts of our own group in these directions will be more fruitful if modified and augmented by those of others.

It is my hope that Grady Reddick, had he been with us, would have enjoyed this presentation. If so, we know that he would have had something pertinent and original to say about it. He was your colleague and mine. He was my friend and yours. He was a wise physician and a brilliant teacher, a kindly gentleman, and a strong man. I shall be permanently grateful to you for this occasion and for this opportunity to join with you in perpetuating his name and in paying tribute to his memory.

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Fundamentals of clinical cardiology

Wolff-Parkinson-White syndrome

*Koo Young Chung, M.D.**
*Thomas J. Walsh, M.D., F.A.C.C.***
*Edward Massie, F.A.C.C., F.A.C.P.****
St. Louis, Mo.

The Wolff-Parkinson-White (WPW) syndrome was first recognized as a clinical entity by Wolff, Parkinson, and White[1] in 1930. The electrocardiographic findings that were later considered to be characteristic of this syndrome were de[scribe]d initially by Wilson[2] in 1915 and Wedd[3] in 1921. This syndrome can be diagnosed only by the electrocardiogram or vectorcardiogram, since in the last analysis the diagnosis rests on the finding of a short P-R interval and prolonged QRS interval due to a delta wave in the electrocardiogram; the latter corresponds to the conduction delay and abnormal *inscription of the initial portion of the* QRSsÊ loop in the vectorcardiogram. Patients with this syndrome are predisposed to recurrent episodes of paroxysmal ectopic tachycardias.[1-4]

The purpose of this paper is to review the previous literature concerning the WPW syndrome, with particular emphasis placed on the occurrence of specific types of ectopic tachycardia in this syndrome and the related electrocardiographic and vectorcardiographic findings. Forty cases of the WPW syndrome collected from the Heart Station and Cardiovascular Laboratories of Barnes Hospital will also be discussed.

General consideration

WPW syndrome has been known as a benign syndrome, and there are no subjective manifestations or hemodynamic disturbances resulting from ventricular pre-excitation itself.[15] However, paroxysmal tachycardia, which tends to be associated with this condition, may come at any time (during rest, exercise, or emotional difficulty, or as a manifestation of allergy[16]) and may begin at birth or during infancy, childhood, or adult life.[4] Sixty to 70 per cent of the cases of WPW syndrome have been found in healthy individuals without organic heart disease.[4,7,9,15,16] The incidence of the WPW *syndrome is difficult* to evaluate because ventricular pre-excitation itself does not produce symptoms unless paroxysmal ectopic rapid heart action develops. Consequently, electrocardiograms are not usually taken in the majority of asymptomatic individuals with WPW syndrome. Frequently, ventricular pre-excitation is found incidentally in electrocardiograms taken for other reasons in later decades.

The incidence of the WPW syndrome has been estimated to be 1.5 per 1,000 patients by Hejtmancik and Herrmann[16] and 0.16 per cent in 67,375 subjects by Averill[17]; there were only 6 cases among

From the Department of Medicine, Washington University School of Medicine, and the Heart Station and the Cardiovascular Laboratory, Barnes Hospital, St. Louis, Mo.
Received for publication June 25, 1964.
*Fellow, National Institutes of Health. Present address: Meharry Medical College, Nashville, Tenn. 37208.
**Assistant Professor of Clinical Medicine.
***Associate Professor of Clinical Medicine.

5 000 patients as reported by Manning[11] and only 2 cases in 1 000 patients studied by Packard and associates[19] An incidence of 0 056 per cent was found by Öhnell[20] and the WPW syndrome was observed in 80 of 50 000 cases reviewed by Katz and Pick[7]

The syndrome occurs more frequently in men than in women with an incidence of between 54 and 70 per cent in males in the various series which have been published[19,11,4] A relatively high incidence of thyrotoxicosis in the WPW syndrome has been reported by different observers[21,22,24] and Master and associates[23] reported that the WPW syndrome disappeared after thyroidectomy was performed to control hyperthyroidism Lepeschkin[25] found thyrotoxicosis in 6 per cent of the patients with the WPW syndrome and stated that the WPW syndrome became manifest as a result of adrenergic preponderance due to hyperthyroidism

Theory and mechanism of WPW syndrome and associated tachycardias

There are different theories in regard to the mechanism of the WPW syndrome and the occurrence of various arrhythmias in this syndrome It is generally agreed that premature activation of a portion of the ventricular myocardium is responsible for the short P R interval the early onset of the QRS deflection with initial slurring (delta wave) and the resultant widening of the ventricular complex characteristic of this condition In Group A the premature activation probably occurs in the left ventricle and in Group B the premature excitation occurs in the right ventricle[11,26] The most acceptable theory at the present time is that involving conduction over an accessory pathway[1,2,23,27,28] Holzmann and Scherf[29] and Wolferth and Wood[7] postulated the bundle-of Kent theory and demonstrated an anomalous A V muscular bundle (in patients who had this condition) similar to that described by Kent[31] in 1893 This theory was further supported by the experimental reproduction of the entire syndrome[4,12,2] and was also proved anatomically by autopsy findings in patients with the WPW syndrome[1,23,30,3,32] Pick[33] stated that anatomic demonstration of an A V bypass was accomplished in over half of the cases examined A muscular communication in the right A V orifice was proposed by Kent[31,34,3] and later by Wolff and associates[1,11] and a communication between the A V node and ventricular musculature was observed by Segers and associates[35] and Scherf and Schonbrunner[36] Öhnell[20] noted a muscular connection between the left atrium and left ventricle which was thought to be congenital[4,9,12] and possibly hereditary[12,21,37,38] since this syndrome was found in infants[7,12,39,40,41] occasionally in premature infants[9] and sometimes was associated with other cardiac malformations[12,4,4,32,42,44] This syndrome has also been observed in several members of one family[12,29,33,37,38]

Rosenbaum[33] pointed out that there may be more than a single anomalous pathway in the WPW syndrome In support of this possibility we have also noted several different kinds of QRS complexes with anomalous A V conduction and different QRSsÊ loop configurations in the same patient[11] Pick[33] stated that an anomalous bypass of the A V node must be present in WPW syndrome since otherwise one could not explain either the occurrence of predominantly supraventricular tachycardias nor the persistence of pre excitation complexes during atrial fibrillation With regard to the mechanism proposed as the explanation of the rapid ectopic tachycardias which occur in the WPW syndrome the re-entry phenomenon has been postulated by different authors[1,7,9] In paroxysmal atrial tachycardia and A V nodal tachycardia a paroxysm of rapid heart action may be precipitated by passage of the ectopic atrial or A V nodal impulse downward through the A V node and its subsequent return to the atria or A V node via the accessory pathway thus constituting a form of re-entry[1] The paroxysmal tachycardia will persist if the re-entry phenomenon is repetitive Consistent with this explanation is the fact that in general the last ventricular beat preceding the onset of an atrial or nodal tachycardia or atrial fibrillation and also the ventricular complexes during the period of tachycardia particularly in paroxysmal atrial tachycardia are

usually not of the pre-excitation type.[4] In paroxysmal atrial fibrillation or flutter the above mentioned re-entry phenomenon alone is not a satisfactory explanation of the mechanism since impossibly high ventricular rates would have to be assumed. However some investigators[6,7] have postulated that the mechanism initiating the paroxysm may be re-entry but that the impulse is returned to the atria very early. If it arrives during the partial refractory or vulnerable period of the atria the re-entry impulse may cause onset of atrial fibrillation or flutter. During these arrhythmias a rapid almost constant stream of atrial impulses passes down either the accessory bundle or the A-V node and bundle branch system depending upon which is less refractory at time of onset of the tachycardia. Normally conducted or pre-excitation QRS complexes may be seen in atrial fibrillation flutter or paroxysmal atrial tachycardia in the WPW syndrome since the impulse may be conducted through either normal or accessory pathways. The impulse in atrial fibrillation may arrive at the A-V node at a rate faster than the normal A-V pathway is capable of conducting since more rapid ventricular rates in atrial fibrillation or flutter in the WPW syndrome show in general anomalous QRS complexes with delta waves[3] although this phenomenon is not always present. From the foregoing observations one is justified in assuming that both conduction systems are capable of transmitting impulses. Another factor that favors the accessory pathway theory is that Pick observed ectopic beats arising from the bypass fibers.[8,9]

Prinzmetal has proposed the theory of accelerated A-V conduction and has stated that the WPW syndrome could be acquired. The evidence in support of his concept is incomplete and inconclusive.[8,10] For that matter it is not logical to expect more rapid A-V conduction in diseased specialized conducting tissue than in the normal when in reality the reverse occurs clinically as is often observed in the case of rheumatic myocarditis or acute myocardial infarction. The theory of an ectopic focus in the right septal mass was proposed by Sodi-Pallares[12] and extrasystoles resembling pre-excitation beats were produced experimentally by him. However Pick was critical of the afore mentioned experimental study because he believed that the rhythm and beats produced represented an artificial A-V dissociation although an irritable ectopic center of impulse formation may be adequate to explain the occurrence of the ectopic tachycardias.[8]

Material and method

The study series consists of vectorcardiograms recorded from 40 patients whose electrocardiograms were considered to be diagnostic according to the criteria currently accepted by the authors which are as follows: (1) short P-R interval of 0.12 second or less in most of the cases; (2) QRS interval between 0.09 and 0.16 second; (3) initial slurring (delta wave) of the QRS deflection occurring on its ascending limb if the major deflection is upward or on its descending limb if the major deflection is downward; (4) secondary S-T segment and T wave changes in the majority of cases; (5) a predisposition to paroxysmal ectopic tachycardia.

In addition the configuration of the QRS deflection in the precordial leads divides the Wolff-Parkinson-White syndrome into two groups[1,5] as follows. In Group A the premature component and the remainder of the QRS complex are primarily upright in both left and right precordial leads. In general Lead V_1 shows R, RS, Rs, RSr and Rsr′ patterns and Lead V_6 shows Rs or R deflections. In Group B the left precordial leads show tall R waves with delta waves in all cases and Leads V_1 and V_2 show delta waves and QRS complexes which are usually resultantly negative. Thus these leads show rS or QS patterns.

The vectorcardiograms were displayed on the Sanborn Viso-Scope in the three standard planes as follows: (1) horizontal, (2) right sagittal and (3) frontal. They were recorded with the corrected lead system described by Frank.[6]

The method of Helm and Fowler[13] was used to determine the vectorcardiographic QRSsÊ-TsÊ angle. The orientation of the vectorcardiogram was expressed in terms of a reference frame divided into −30 degree segments in a counterclockwise

Table I Electrocardiographic and vectorcardiographic analysis of patients with Wolff Parkinson White syndrome

		Group A			*Group B*		
P R interval (sec)	0 08 or less		3			2	
	0 09 0 10		5			12	
	0 11 0 12		6			7	
	0 13 or more		2			3	
QRS interval (sec)	0 10 or less		2			11	
	0 11 0 12		7			8	
	0 13 or more		7			5	
Delta wave interval by ECG (sec)	0 02 or less		2			3	
	0 03 0 04		5			11	
	0 05 0 06		7			7	
	0 07 or more		2			3	
Conduction delay by VCG (sec)	0 02 or less		2			12	
	0 03 0 04		5			6	
	0 05 0 06		3			2	
	Entire efferent limb		6			4	
Direction of delta wave (initial vector)	Ant Sup Left		7			8	
	Ant Inf Left		6			5	
	Ant Sup Right		1			0	
	Ant Inf Right		2			0	
	Post Sup Left		0			3	
	Post Inf Left		0			8	
Inscription of QRS Ê loop		*H*	*S*	*F*	*H*	*S*	*F*
	C	3	7	8	1	15	4
	C/CC	0	5	3	2	4	2
	CC	7	3	2	17	2	17
	CC/C	6	1	3	4	3	1
Spatial QRS Ê TsÊ angle (degree)	0 30		3			1	
	31 60		6			3	
	61 90		3			2	
	91 120		0			3	
	121 150		3			9	
	151 180		1			6	

C Clockwise *C/CC* Clockwise [illegible] limb [illegible] counterclockwise [illegible] limb *CC* Counterclockwise *CC/C* [illegible] clockwise [illegible] limb [illegible] *H* Horizontal *S* Sagittal *F* Frontal

direction and +30 degree segments in a clockwise direction from 0 to 180 degrees Thus 0 degree in the reference frame is situated to the left (the observer's right) in the frontal and horizontal planes and anteriorly in the right sagittal plane +90 degrees is located inferiorly in the frontal and sagittal planes and anteriorly in the horizontal plane

The hospital charts of all 40 patients in this series were reviewed Twenty nine of the subjects were males and 11 were females The ages of these patients varied between 4 and 19 years

Results

Table I summarizes the electrocardiographic and vectorcardiographic findings of the 40 patients whose electrocardiograms were considered to be compatible with the diagnosis of ventricular pre excitation Sixteen electrocardiograms and vectorcardiograms exhibited the Group A ventricular pre excitation pattern and 24 showed the Group B variety

Electrocardiographic findings

P R INTERVAL The P R intervals in the 40 electrocardiograms varied between 0 06 and 0 14 second with those of Gr B

showing shorter P-R intervals than those of Group A. The majority of the 40 cases had intervals between 0.09 and 0.12 second. The P-R intervals were 0.13 second or more in 5 of our cases, the longest interval being 0.20 second without any demonstrable disease. Similar cases have been reported both in healthy[4,16] and diseased hearts.[16,18] The P-R intervals were 0.12 second or less in 35 cases (87.5 per cent) of our series, which is somewhat similar to the findings in Wolff's study.[4]

QRS INTERVAL. The QRS intervals of the 40 electrocardiograms varied between 0.08 and 0.16 second on the whole. The QRS intervals in the Group B tracings generally were shorter than those in the Group A electrocardiograms. 11 of the 24 Group B cases revealed QRS intervals of 0.10 second or less.

The QRS intervals were 0.10 second or less in 13 cases (32.5 per cent) of our series, which is similar to what Grant and associates[7] reported. It was interesting to note that about half of the Group B cases showed normal QRS intervals with delta waves, whereas the majority of Group A electrocardiograms showed prolonged QRS intervals with delta waves.

DELTA WAVE. All electrocardiograms showed some degree of slurring of the initial portion of the QRS complexes, with delta wave durations varying between 0.02 and 0.08 second. The usual value of the pre-excitation interval was between 0.03 and 0.06 second.

QRS COMPLEX CONFIGURATION. In Group A, the majority of electrocardiograms showed R, Rs, or RS patterns in Lead V_1 and Rs or R complexes in Lead V_6. In Group B, the majority of records showed a QS or rS pattern in Leads V_1, and an R wave in Lead V_6 in all cases.

Vectorcardiographic findings. The WPW syndrome has been studied vectorcardiographically by a number of different authors.[3, 11,16,17] The over-all results of our vectorcardiographic study are presented in Table I and Fig. 1. The vectorcardiograms of the 40 patients comprising the study series were divided into Groups A and B according to the characteristics of the QRS-Ê loop.[11,3] There were 16 patients with Group A vectorcardiograms and 24 patients with Group B vectorcardiograms. It should be noted that the values for range in orientation of the mean vectors are intended to be read in a clockwise direction in the appropriate reference frame.

INITIAL CONDUCTION DELAY AND THE DELTA VECTOR OF THE QRS-Ê LOOP. The initial conduction delay was much more marked in Group A than in Group B. Six of the 16 Group A cases showed conduction delay involving the entire efferent limb. The initial conduction delay was less than 0.03 second in half of Group B, whereas such a finding was made in only 2 cases of Group A. It is interesting to note that there was a discrepancy in the duration of the conduction delay between the electrocardiographic and vectorcardiographic findings, as shown in Table I. The delta vector* was directed anteriorly, either superiorly or inferiorly, and to the left in the majority of cases (26 patients) in both groups. Less than one half of the Group B vectorcardiograms had delta waves directed posteriorly and to the left and either superiorly or inferiorly.

PLANAR QRS LOOPS

1. Horizontal QRS loop. The maximal mean instantaneous QRS vector was oriented between +18 and +90 degrees (average +47 degrees) in Group A, and between −55 and +38 degrees (average −8 degrees) in Group B.

2. Right sagittal QRS loop. The maximal mean instantaneous QRS vector varied widely, ranging between −125 and +75 degrees (average +4 degrees) in Group A and between +15 and −15 degrees (average +175 degrees) in Group B.

3. Frontal QRS loop. The maximal mean instantaneous QRS vector ranged between −120 and +72 degrees (average +5 degrees) in the Group A cases, and between −45 and +40 degrees (average +5 degrees) in Group B cases.

The average orientation of the maximal QRS vector in the horizontal plane was quite different in both groups, but the average orientation of the maximal QRS vector in the frontal plane in the two groups was the same.

INSCRIPTION OF THE QRS-Ê LOOP

1. Horizontal plane. The QRS-Ê loop

*The delta vector was measured as the terminal vector of the initial segment of the QRS loop showing conduction delay.

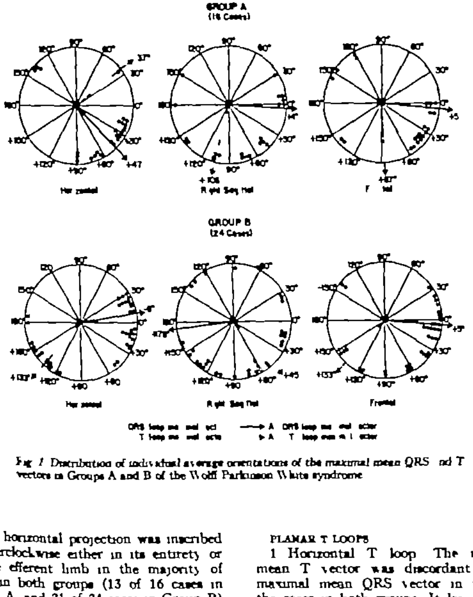


Fig 1 Distribution of individual average orientations of the maximal mean QRS and T vectors in Groups A and B of the Wolff Parkinson White syndrome

in the horizontal projection was inscribed counterclockwise either in its entirety or in the efferent limb in the majority of cases in both groups (13 of 16 cases in Group A and 21 of 24 cases in Group B) (See Table I)

2 Right sagittal plane The majority of cases showed clockwise inscription of either the entire loop or of the efferent limb in both groups (12 of 16 cases in Group A and 19 of 24 cases in Group B)

3 Frontal plane The QRSsÊ loop in the frontal projection was inscribed clockwise in Group A (8 of 16 cases) and counter clockwise in Group B (17 of 24 cases)

The QRSsÊ loop showed a figure of eight inscription in at least two planes (clockwise in the efferent limb and counter clockwise in the afferent limb or vice versa) in about one half of Group A cases but in only one fourth of Group B cases

PLANAR T LOOPS

1 Horizontal T loop The maximal mean T vector was discordant to the maximal mean QRS vector in most of the cases in both groups It lay between −145 and +70 degrees (average −37 degrees) in Group A cases and between −30 and −125 degrees (average +133 degrees) in Group B cases

2 Right sagittal T loop The maximal mean T vector had a wide range of orientation in both groups just as was the case with the maximal vector of the right sagittal QRS loop The average orientation of the maximal mean T vector was +106 degrees in Group A and +45 degrees in Group B cases

3 Frontal T loop The maximal mean T vector was discordant to the maximal mean QRS vector as in the horizontal plane and it lay between 0 and −120 de

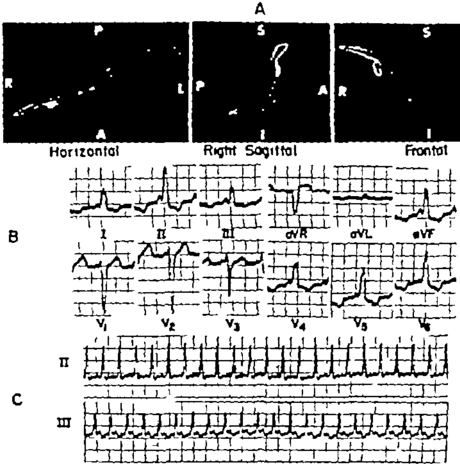


Fig. 2. Typical Group B WPW syndrome shown vectorcardiographically and electrocardiographically. The QRS-Ê loop is displaced posteriorly, inferiorly, and to the left. There is marked conduction delay in the entire efferent limb of the QRS-Ê loop. The T-Ê loop is 180 degrees discordant to the QRS-Ê loop and an ST vector is also present. The lower two lead strips show paroxysmal atrial tachycardia (PAT) with a rate of 23 per minute. Note that the QRS complex during the PAT exhibits normal A-V conduction.

grees (average +87 degrees) in Group A and between +55 and −140 degrees (average +133 degrees) in Group B.

SPATIAL QRS-Ê T-Ê ANGLES. Group B vectorcardiograms presented wider spatial QRS-Ê T-Ê angles than did the Group A vectorcardiograms. In the majority of Group B cases (20 of 24) the angles exceeded 60 degrees, whereas in more than one half of the Group A cases (9 of 16) the spatial QRS-Ê T-Ê angle was less than 60 degrees.

We have been unable to attach any clinical significance to the finding of a narrow QRS-Ê T-Ê angle in the Group A cases or to a wider angle in the Group B cases.

The vectorcardiographic findings in this study are somewhat different from those encountered in our previous observations[3] or in the reports of other investigators,[5-14] probably because of the different lead systems utilized.

Arrhythmias

It is a well-known fact that recurrent episodes of paroxysmal tachycardias[1,2] accompany the Wolff-Parkinson-White syndrome in a high percentage of cases. Wedd[3] first called attention to the occurrence of paroxysmal tachycardia in this syndrome in 1921. The frequency of tachycardia varies between 40 and 80 per cent in the reports of many different authors.[4, 12-16] Our study showed an incidence of 70 per cent (29 of the 40 cases), which agrees with that of Wolff.[4,12] The type of tachy-

cardia in the Wolff-Parkinson-White syndrome is a rapid regular supraventricular tachycardia in the majority of cases.[4,7,9,11] In our study, 24 (82 per cent) of 29 patients had paroxysmal atrial tachycardia (Figs. 2, 3, and 4).

The incidence and types of paroxysmal ectopic tachycardias are summarized in Table II. There were additional patients with histories of unobserved episodes of rapid heart action that may or may not have been ectopic tachycardia, but these were excluded from this series since we were interested only in documented or observed tachycardias.

Atrial fibrillation and atrial flutter were rather uncommon in our experience[8,11] in cases of the Wolff-Parkinson-White syndrome, although these arrhythmias have been reported by others.[1,5,9,24,46,61] If atrial fibrillation or flutter occurs, it is frequently associated with rheumatic heart disease.[7,9,11] However, atrial fibrillation with rapid ventricular response can occur in the WPW syndrome without any organic heart disease;[1,4] this was the case in one of the patients in our series. Atrial flutter is encountered far more rarely in the WPW syndrome than is atrial fibrillation.[1,7,9,37] In our study, 4 patients (13.7 per cent) had atrial fibrillation, and their electrocardiographic and vectorcardiographic patterns belonged in Group A (Fig. 5 and Table II). One of the 4 patients had rheumatic heart disease in addition to the WPW syndrome. There was no significant difference in the incidence of the tachy-

Table II. The occurrence of various arrhythmias in the Wolff-Parkinson-White syndrome

Arrhythmia	Group A	Group B
Paroxysmal atrial tachycardia	10	14
Atrial fibrillation	4	0
Atrial flutter	1	0
Ventricular premature contraction	0	1
Nodal premature contraction	2	
Ventricular parasystole	0	1
Atrial parasystole	1	0

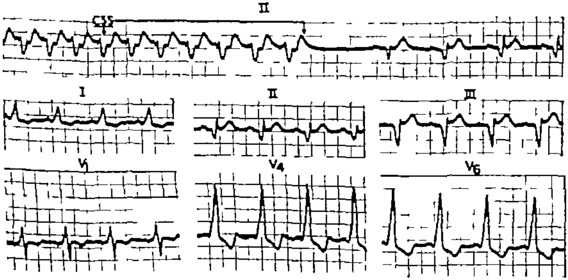


Fig. 3. The first portion of the upper strip of Lead II shows paroxysmal atrial tachycardia with a rate of 140 per minute and then the rhythm is converted by carotid sinus stimulation to sinus rhythm with the anomalous AV conduction which was seen prior to the onset of the paroxysm of tachycardia. The QRS complex during the tachycardia is different from the QRS complex during sinus rhythm in that it is wide and bizarre, a finding which may represent ordinary aberrant ventricular conduction. (This case was previously presented in electrocardiographic form in *Clinical Vectorcardiography and Electrocardiography* by Edward Massie, M.D., and Thomas J. Walsh, M.D., Chicago, 1960, The Year Book Publishers, Inc.)

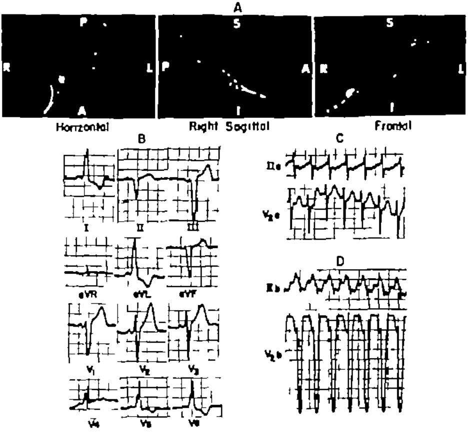


Fig 4 The vectorcardiogram (*A*) and electrocardiogram (*B*) display Group B ventricular pre-excitation *There is marked conduction delay in the entire efferent limb of the QRS-Ê loop* The T Ê loop is 180 degrees discordant and there is an ST vector The lead strips in *C* and *D* were taken on different occasions in this patient The leads in *C* show paroxysmal atrial tachycardia (PAT) with a rate of 170 per minute and normal QRS complexes without anomalous conduction The tracings in *D* demonstrate PAT with a slightly faster rate (175 per minute) than that in *C* and the QRS complex is markedly aberrant

cardia between Group A and Group B patients The ventricular rates in the entire group with ectopic tachycardias varied between 160 and 200 per minute Only one of our series had atrial flutter (with 2 1 atrioventricular response) (Fig 6) This 58 year-old patient had arteriosclerotic heart disease his electrocardiogram and vectorcardiogram presented the findings of Group A A similar case has been reported previously [illegible] None of the Group B patients showed atrial fibrillation or flutter (see Table II) It is impossible to evaluate the true incidence of atrial flutter or fibrillation in the two groups (A and B) of the Wolff Parkinson White syndrome in the literature since the majority of case reports fail to show precordial leads or vectorcardiographic findings that permit one to determine the group type

The QRS complex during paroxysmal tachycardia in the WPW syndrome is normal in the majority of cases of regular supraventricular tachycardia[illegible] (see Fig 2) although there are exceptions[illegible] (see Figs 3 and 4) this is particularly true in atrial fibrillation (see Figs 5 and 7) or atrial flutter[illegible] (see Fig 6) in which the QRS deflection may simulate ventricular tachycardia[illegible] Paroxysmal atrial tachycardia with anomalous A V excitation was reported by Rosenbaum[illegible] Scherf and Schonbrunner[illegible] were the first to point out the occurrence of wide QRS complexes during paroxysmal atrial fibrillation or flutter Although the occurrence of ven

tricular tachycardia in the WPW syndrome has been reported by several observers,[11,17,21] we have been unable to find a single unequivocal case of the arrhythmia in the WPW syndrome. Wolff[4] has stated that the most likely diagnosis of the arrhythmias in these reports was rapid atrial fibrillation or flutter with anomalous conduction instead of ventricular tachycardia (see Figs 5 and 7). Ordinary aberrant ventricular conduction without anomalous conduction may occur in paroxysmal atrial tachycardia[18] (see Fig 3), atrial fibrillation (see Fig 5) or atrial flutter because of the rapid rate. This aberration of the QRS complexes may occasionally simulate ventricular premature beats or ventricular tachycardia.[6,17,23] Fig 5 is a good example of atrial fibrillation with rapid ventricular response (rate between 170 and 270 per minute) with marked aberrant ventricular conduction producing QRS complexes of a form different from that of those seen during sinus rhythm with the Wolff Parkinson White syndrome. These ventricular deflections closely resemble ventricular tachycardia in some portions of the electrocardiogram. The occurrence of more than one type of abnormal ventricular complex in different paroxysms of rapid heart action

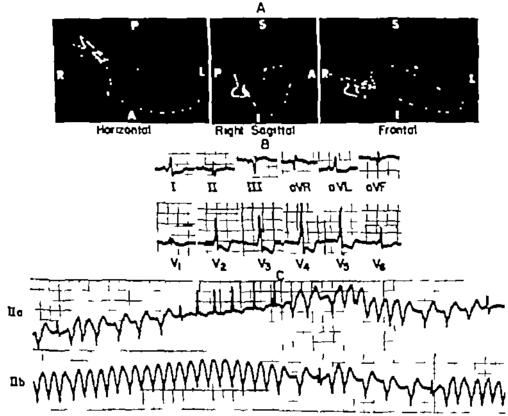


Fig 5 The vectorcardiogram (A) and electrocardiogram (B) show the Group A WPW syndrome. The lower two tracings (C) are continuous strips of Lead II during paroxysmal atrial fibrillation with a rate of 170 to 270 per minute. In these strips there are many different forms of QRS complexes. Some portions of Lead IIb show a very rapid ventricular rate (270 per minute) with marked aberrant ventricular conduction of the ventricular deflection which differs from the QRS complexes of the anomalous beats. These areas resemble ventricular tachycardia but probably are the result of markedly exaggerated anomalous A V conduction. (Some QRS complexes such as the second, ninth and twenty-seventh beats of Lead IIa and the thirtieth beat of Lead IIb are similar to the QRS complexes during normal sinus rhythm.) The QRS complexes in the mid portion of Lead IIa show normal QRS complexes without anomalous A V conduction. The occurrence of QRS complexes of various configurations indicates that the impulses travel through the normal A V pathway and/or the anomalous A V pathway.

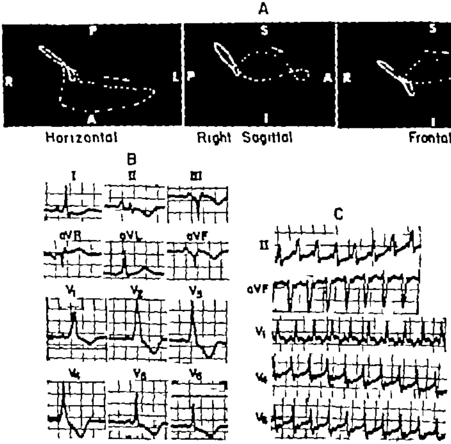


Fig 6 The vectorcardiogram and electrocardiogram (A and B) exhibit the Group A WPW syndrome There is conduction delay in the initial 0 03 second of the QRSsE loop and the T sE loop is almost 180 degrees discordant to the QRSsE loop C shows atrial flutter with 2 1 AV conduction best seen in Lead V The atrial rate is about 400 per minute (The QRS complexes during paroxysm are similar to the QRS complexes during sinus rhythm)

has been observed previously[4,8] and one example is shown in Fig 4 In this figure two tracings taken at different times show two different QRS complexes occurring with very similar rates in a case of paroxysmal atrial tachycardia associated with the Wolff Parkinson White syndrome Different kinds of atrial arrhythmias (paroxysmal atrial tachycardia atrial fibrillation and atrial flutter) have been observed on different occasions in the same individual who had the WPW syndrome[7,9]

Paroxysmal tachycardias in association with the Wolff Parkinson White syndrome have a much higher incidence in infants and young children than in adults and usually they are very rapid regular supraventricular tachycardias[7,8,40,4] Isolated nodal premature beats or nodal escape beats with normal QRS complexes[18,27,44] as well as with anomalous AV conduction[7,38,75] have been reported in the Wolff Parkinson White syndrome In our series there were 4 cases of nodal premature beats and all showed normal QRS complexes The occurrence of ventricular premature beats in the WPW syndrome has been reported[8,17,78] and one of our patients a young healthy individual presented continuous ventricular bigeminy and intermittent atrioventricular nodal rhythm with atrioventricular dissociation (Fig 8 A) We found one ventricular parasystole (Fig 8 B) in an elderly individual who had coronary heart disease associated with the Wolff Parkinson White syndrome and this has been reported by others[7,18,18,17,77] One atrial parasystole (Fig 8 C) was also found in an elderly woman who had breast cancer and mild arteriosclerotic heart

disease and this is a rare combination in so far as we can ascertain. Ventricular parasystole in general occurs once in 900 to 1,200 (0.1 per cent) routine electrocardiograms taken in a general hospital,[75,76] whereas the Wolff-Parkinson-White syndrome has an incidence of 0.15 to 0.2 per cent.[7,11,17,18] Therefore, the combination of parasystole and the Wolff-Parkinson-White syndrome is very rare indeed.

Various other arrhythmias, such as first-degree[4] and second-degree A-V block,[2,3,28,4] complete atrioventricular block,[12] and atrioventricular nodal rhythm[18] have also been reported.

Effect of drugs and other procedures on WPW syndrome and associated arrhythmias

If patients with the WPW syndrome develop paroxysmal tachycardia, they may require urgent medical treatment, and the paroxysm almost always induces congestive heart failure in infancy, early childhood,[18] or in older patients with heart involvement. About one half of the patients in our series did not require any medical treatment for their paroxysmal tachycardia. In the remainder, quinidine (sometimes Pronestyl) or digitalis or a combination of the drugs, carotid sinus pressure and atropine were used in the various arrhythmias associated with the WPW syndrome. Hejtmancik and associates[7] reported 80 cases of paroxysmal tachycardia with the WPW syndrome and in most of their patients the rapid ectopic tachycardia reverted spontaneously to sinus rhythm.

Wolff[1] observed that most of the ectopic tachycardias ended spontaneously, or as a result of the patient holding his breath, lying down or vomiting, or by stimulation of the carotid sinus or the use of drugs.

Various medications such as digitalis, quinidine, Pronestyl, acetylcholine, neostigmine, atropine, amyl nitrite, potassium salts, or any combination of these preparations have been employed in the treatment of the ectopic tachycardias associated with the WPW syndrome.[1,17,22,18] However, the drugs are not always effective in the treatment of rapid heart action, and this is not surprising, since the underlying pathophysiology of the syndrome is not completely settled[18] and the effect of antiarrhythmic agents may vary in the presence of various types of myocardial and conduction abnormalities.

Digitalis. Digitalis is the drug of choice in the treatment of regular paroxysmal supraventricular tachycardia since it predominantly depresses the normal conduction system,[3] that is, it is capable of prolonging or completely blocking conduction in the A-V node and bundle of His.[4] There is some evidence that digitalis increases the excitability of the anomalous conduction system and may aggravate the arrhythmia.[11,7] Consequently, this medication usually fails to slow the rapid ventricular rate in atrial fibrillation with WPW syndrome.[3,11,1,18,19]

Often large doses of digitalis are required for the treatment of rapid heart action and may induce digitalis toxicity, particularly in cases of refractory arrhythmias associated with the WPW syndrome.[3]

Quinidine and procaine amide. In atrial fibrillation, quinidine or procaine amide invariably causes the pre-excitation QRS complex to disappear, since it depresses conduction via the accessory pathway, thereby favoring normal A-V conduction without changing the transmission interval.[11] Quinidine blocks the action of the vagus nerve on the heart, and its effect is similar to that of atropine, but less pronounced.

Hejtmancik and associates[18] treated successfully with intravenous injections of procaine amide 2 patients who had paroxysmal atrial tachycardia associated with the WPW syndrome. It appears that the best results are achieved by giving digitalis and quinidine (or occasionally procaine amide) simultaneously for paroxysmal ectopic tachycardia associated with the WPW syndrome, particularly in the case of atrial fibrillation or flutter.[7,8]

Carotid sinus stimulation. Carotid sinus pressure can abolish the ventricular pre-excitation[12,11] or, in occasional instances, may cause it to appear.[1,12,1] When carotid sinus pressure is applied in the presence of WPW syndrome, it can produce an A-V nodal rhythm with a normal QRS complex,[18] since the vagal stimulation tends to prolong A-V conduction time or rarily block the normal pathway

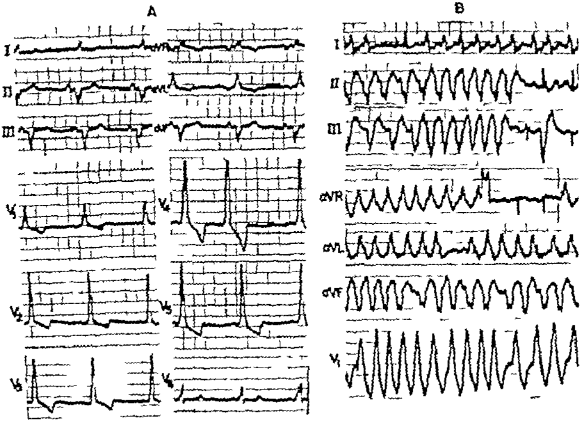


Fig. . Electrocardiogram A presents typical Group A ventricular pre-excitation and B exhibits atrial fibrillation with rapid ventricular response (rate varies between 180 and 230 per minute). The QRS complexes during the paroxysms of rapid ventricular response predominantly demonstrate exaggerated anomalous conduction. Some QRS complexes such as the third beat of Lead I, the twelfth and thirteenth beats of Lead II, the eleventh and thirteenth beat of Lead III, and the tenth and eleventh beats of Lead aVR show a normal configuration without anomalous conduction. This is a very common finding before and/or after the onset of paroxysmal tachycardia in the WPW syndrome.

place the pacemaker from the S-A node to the A-V node.[4] Pick and Katz[4] observed that in one patient with paroxysmal atrial tachycardia with 1:1 conduction associated with the WPW syndrome, carotid sinus pressure induced paroxysmal atrial tachycardia with varying A-V response which subsequently changed to atrial flutter and finally to atrial fibrillation.

One of the patients of our series who had paroxysmal atrial tachycardia in association with the WPW syndrome (Fig. 3) was unaffected by a combination of digitalis and quinidine but responded very well when carotid sinus stimulation was added.

Exercise. Exercise may re-establish normal A-V conduction, since the abnormal pathway is usually unable to function above a critical heart rate.[59]

Wolff[18] reported the disappearance of the WPW syndrome when exercise raised the heart rate to 120 to 140 per minute, whereas Sanghvi[14] found that exercise caused WPW conduction in successive beats in one case. Sandberg,[11] in a study of 28 cases of WPW syndrome,[3] found that 10 patients were transitorily affected by exercise in variable fashion.

Various other drugs. The administration of atropine has been commonly used to produce normal conduction in cases of WPW syndrome.[9,17] The development of A-V dissociation after the administration of atropine in WPW has been reported.[17] Bellet[39] observed that antithyroid drugs and I[131] may be effective in some refractory cases of paroxysmal tachycardia with the WPW syndrome. In addition, neostigmine, acetylcholine, amyl nitrite, and potassium

salts may abolish the tachycardia.[36] Fisch and associates[9] have used external counter shock successfully for supraventricular tachycardia associated with WPW syndrome and in light of present knowledge it appears to be advisable to apply this form of therapy when urgent treatment is needed.

Prognosis

The prognosis of uncomplicated WPW syndrome is generally good unless rapid heart action occurs very frequently and the episodes are long in duration. Paroxysmal tachycardia may produce diminished mental alertness, loss of consciousness, and in patients with underlying coronary heart disease, episodes of coronary insufficiency which require urgent medical attention.

Sudden death during or after the episode of tachycardia has been reported, and the paroxysm itself may frequently cause congestive heart failure and sometimes irreversible changes in the heart.[36]

The occasional occurrence of tachycardia

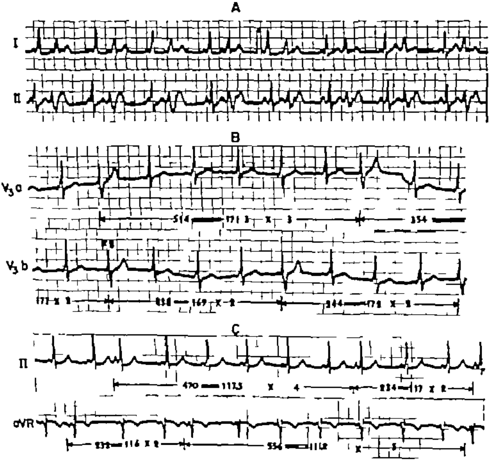


Fig. 8. Parts A, *B*, and *C* are tracings from three different patients. A. The electrocardiogram illustrates ventricular pre-excitation with frequent ventricular premature beats producing ventricular bigeminy and an intermittent A-V nodal rhythm (the eleventh, thirteenth, and fifteenth beats of Lead I, the first, third, fifth, and seventh beats of *Lead II*) causing A-V dissociation. (Modified from Fig. 345, page 493 in *Clinical Vectorcardiography and Electrocardiography* by Edward Massie, M.D., and Thomas J. Walsh, M.D. Chicago, 1960, The Year Book Publishers, Inc.) *B*. Lead V_3a and V_3b are continuous. These strips show ventricular pre-excitation with intermittent ventricular parasystole. The rate of the parasystole is 37 per minute. There is a ventricular fusion beat (marked *FB*). *C*. This tracing displays ventricular pre-excitation with intermittent atrial parasystole. Note that the ventricular complexes of the parasystolic beats also show anomalous A-V conduction. The rate of the atrial parasystole is 52 per minute.

in individuals who have a normal heart and the WPW syndrome has no significant effect on the cardiovascular system, so that these persons usually lead normal active lives.[17] The prognosis is almost always serious when the syndrome occurs during infancy or early childhood, or in adults with heart involvement when the attack of tachycardia is refractory to therapy and complications ensue.

Summary and conclusions

Previous literature concerning the WPW syndrome has been reviewed. In addition, 40 of our cases have been studied in detail with particular emphasis on the occurrence of various arrhythmias and vectorcardiographic analysis. No difference was found in the incidence of regular supraventricular tachycardia (paroxysmal atrial tachycardia) between patients with Group A ventricular pre-excitation and those with Group B type, but atrial fibrillation or flutter was found only in Group A patients.

There was a significant difference in both groups between the duration of the initial portion of conduction delay in the electrocardiogram and that in the vectorcardiogram. In addition, Group A electrocardiograms and vectorcardiograms tended to show more marked initial conduction delay. The spatial QRS-Ê T-Ê angle was much narrower in Group A (less than 60 degrees) than in Group B vectorcardiograms. However, we have been unable to establish that either a narrow or wide QRS-Ê T-Ê angle has any clinical significance.

There is much evidence to justify acceptance of the accessory pathway theory as the mechanism of the Wolff-Parkinson-White syndrome and of the associated arrhythmias, but other theories have been discussed.

The treatment of choice for paroxysmal supraventricular tachycardia in Wolff-Parkinson-White syndrome is either digitalis or quinidine in the majority of cases, whereas atrial fibrillation and atrial flutter usually require a combination of both medications. External countershock seems to be an appropriate treatment when the patient's condition is apparently deteriorating.

Twenty-six patients (65 per cent) in our series showed no evidence of organic heart disease, which is similar to the findings reported by others.[13,14] Most of the patients with organic heart disease were more than 45 years of age, and the majority of these had some evidence of arteriosclerotic heart disease and/or hypertensive cardiovascular disease. There were 4 other patients, including one who had mitral stenosis due to rheumatic fever (this patient had atrial fibrillation with rapid ventricular response on many occasions), 2 with thyrotoxicosis, and 1 with congenital heart disease (interatrial septal defect).

One of the more interesting findings in this study was that 10 patients with the WPW syndrome (25 per cent) had psychiatric disorders (mainly manic-depressive psychosis). This finding may be a coincidental manifestation, since we cannot explain the reason for such an association, but a similar observation was described by Hejtmancik and associates[16] in 1957 and deserves further investigation.

Two instances of the very rare combination of parasystole and Wolff-Parkinson-White syndrome have been described, and in so far as we are able to ascertain, the example of a combination of atrial parasystole with the Wolff-Parkinson-White syndrome may be among the first such cases reported.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Alan F. Lyon

Diuretic therapy

Part VIII Triamterene as a diuretic

Joseph J. Seller, M.D.
Arthur C. DeGraff, M.D.
New York, N.Y.

When triamterene [illegible] first [illegible] diuretic it was [illegible] aldosterone antagonist because [illegible] potassium retention [illegible] urinary excretion of sodium and chloride without proportional change in the excretion of potassium. It has now been established that its renal effect is like spironolactone but, unlike spironolactone, it is not an aldosterone antagonist.

Although triamterene causes an increase in the excretion of sodium in adrenalectomized human [illegible] on a normal intake, it does cause reversal of the retention of sodium induced by aldosterone and increases the excretion of sodium in adrenalectomized dogs sustained on a high sodium diet with no steroid supplementation. Triamterene causes a decrease in the excretion of potassium in normal and adrenalectomized rats with or without the administration of aldosterone. Thus triamterene acts independently of aldosterone in rats. It has also been shown that triamterene causes a natriuresis in sodium-deprived as well as sodium-loaded rats with intact adrenal glands, which suggests that the diuretic effect is independent of the stimulus to the production of aldosterone.

Similarly, the studies of triamterene in man have shown that it causes a diuresis associated with increased excretion of sodium and decreased or unchanged excretion of potassium. When sodium and water are restricted, triamterene causes a greater [illegible] natriuresis, but the [illegible] excretion of potassium occurs in the patient who are not restricted in their intake of salt and water. It has also been shown that triamterene does not alter the rate of excretion of Porter-Silber [illegible] and [illegible] ketosteroid and it does completely antagonize the sodium-retaining activity of compound F. For all the above-mentioned reasons it is generally accepted that triamterene affects renal function in the human being like an aldosterone antagonist, although its activity is not dependent upon the presence of aldosterone. The conclusion is that it is an inhibitor of the renal transfer of sodium and potassium, probably acting in the distal renal tubules. Stop-flow analysis also suggests that it has a distal site of action where it produces decreased excretion of potassium from the tubular cell to the tubular lumen.

When administered orally to man, it appears in the urine within 15 minutes and may impart a blue fluorescence to the urine. Peak levels are present in the blood in 6 to 8 hours, and the drug is almost undetectable at 24 hours. It begins to enhance

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[illegible]
Department of [illegible] New York [illegible] New York, N. Y. [illegible]

diuresis in 2 hours with peak output occurring within 10 hours. After 16 hours the urinary output returns to the control level. There is a double peak of elimination of sodium and water with concomitant decreased excretion of potassium at 4 and 10 hours. Since this does not fit the time of the normal diurnal variation it has been suggested that this may reflect an enterohepatic recirculation. The diuretic effect does not outlast the elimination of the drug from the body. Triamterene is distinguished from spironolactone by its rapid onset of action and its abrupt termination of effect. It is of interest that the diuretic effect of triamterene like that of mercurials is completely counteracted by BAL.

Its diuretic effect can be enhanced by combination with spironolactone. For instance given to a normal patient on a low sodium diet the natriuretic effect of combined small doses of triamterene and spironolactone is greater than that of much larger doses of either drug administered separately.

In animals triamterene increases the natriuresis caused by chlorothiazide and benzthiazide and decreases their kaliuretic effect. In man in comparable doses triamterene is not so effective as a typical thiazide diuretic such as hydroflumethiazide. Although hydroflumethiazide causes greater excretion of sodium than does triamterene and triamterene causes less excretion of potassium than does hydroflumethiazide the effect of their combination is to increase the excretion of sodium and water without increasing the excretion of potassium over the control. Furthermore triamterene produces an additional diuresis when given after a combination of hydroflumethiazide and spironolactone in maximally effective doses.

The drug has not been adequately studied in all types of pathologic retention of fluid. Alone or in combination it has been effective in most cases. The more dramatic effects are seen in patients who have been refractory to other diuretics and who are believed to have significant hyperaldosteronism such as in liver disease with ascites.

Careful assessment of dose response has suggested a dose of 60 mg per square meter of body surface or an average of 100 mg per person. However there have been reports of increased response to doses as high as 400 mg in some edematous patients.

There is a tendency for triamterene to increase serum potassium particularly in the higher doses although this has never been reported to be symptomatic. In doses of 200 mg daily the serum potassium may be elevated in 10 per cent of the patients. Studies of potassium balance suggest that this elevated serum potassium might be at least in part accounted for by a shift from the intracellular to the extracellular compartment. This has been found to make this drug effective in the treatment of patients with familial periodic paralysis in which a shift of potassium from the extracellular to the intracellular compartment is the immediate cause of symptoms. In the few instances in which triamterene was evaluated in patients with diabetes insipidus in which condition thiazides are effective no effect was noted.

Although there have been references to mild hypotensive effects of triamterene in hypertension careful studies of the drug used as the sole agent are still lacking. Its effectiveness has not been impaired when it was used in combination with hydrochlorothiazide and fewer instances of hypokalemia have been noted with the drugs combined than with hydrochlorothiazide alone.

As with most other effective diuretics elevation of the blood urea nitrogen in association with the use of triamterene has been reported. Two problems common to thiazide diuretics are hyperuricemia and hyperglycemia. In past experience hyperuricemia has occurred in as many as 60 per cent of the patients on thiazide diuretics and impaired glucose metabolism has occurred in as many as 50 per cent of such patients. Analysis of our own data has shown that no more than 17 per cent of the patients on triamterene developed hyperuricemia. This would be in keeping with reports of increased excretion of uric acid in patients on triamterene. Only 5 per cent of our patients have been noted to have elevation of fasting blood sugar on triamterene. In the past there have been attempts to link abnormalities of the uric acid and sugar with the loss of [illegible]

Annotations

Concepts of "primary hypertension" and their epidemiological significance

There are probably only three major views on the pathogenesis of primary or essential hypertension. At some time with varying enthu ia m I may have defended each. What I now propose as accessible to potentially productive epidemiologic analy is is largely a matter of emphasis with regard to one of these. The basic premises are that it fruitless to approach an arr y or even a pair of problems with a single hypothesis nd that it is likely that there are several kind of or at least more than one pri mary hypertension.

The first view that this is n entity a specific disease that has its origin in some more or le supposed unphysiologic mechanism Th is rem nis cent of the systems of pathogenesis that ascribed d sease to worms in the blood or to devil and is the sort of concept that would extend to credence were manometer more widely av ilable to witch doctors It is di concerting to realize that something along this line is fairly widely held I th se who have manometers and know how to use them It is what S George Pickering alled the old idea that the disease represent a qu litative deviation f om the norm unique fault (w th) a unique and specific ca se.

The second view h h he term the new idea is that essential h pe tension a quant tative deviation from the rm nd that t n age conditioned graded haracteri t n the d stribu tion of arterial press u It is t ll a I ease more those who h e t often t id t troubl some and need treatment t relie o pr nt the ascular disease th t t cog nder id I te How ever unlike the sec nd ty hypert ns n th there is no single prim I turb I be evidence for this view deriv f m th orres hat showed t at unimodal frequ nc I t ibut of pre sure by age Those who oppose the k I ok for bi modality in d str but o urv nd w th me se lection f nd them I part I ker ng pos tion is philosoph ace be urre t f xt te that the greatest cont but the san tation of the mind would be the h lition of th term normal and physiologic I nd the app al Th ma have merit but the pt le es I ar direction for epidem l g studi I r I t unde tand ing of mechani ms.

The th d vi) P ge mosaic theory This desc ibe events I h pe ten on as a mult fact al proce th t esult f om co of fact among which one or even n one (may be) more or less dominant V l cker ing has pointed out this resembles his view n several respects notably in that it doe n t postu late a single or even an abnormal mech ni m It takes into account the whole tessellated arr y of factors intrinsic and extrinsic that have to do with regulation of arterial pres ure Because it is based on physiologic considerations it would seem at the outset to be more realistic than a view based on n array of pressures in outpatients ome of which may have been disturbed by apprehension tuber u lous or renal arterial stenoses Unfortunately the mosaic theory involves so many organs and sy tems and so many biologic d sciplines that it has been criticized as more of an unanswerable rhetori cal device than a hypothesis This critici m over looks the fact that what is under con ider tion is *established* and not *incipient* hypertension and that it is very likely that in primary as in secondary hypertensions the establi hed disease invol es all or most pressure regulating mechanisms From the aspect of epidemiologic study the concept offers little unless attention is concentrated on those early stages of the process when some dominant disturbance may still be recognizable.

The first or d ond approach can be disca ded except in the secondary hypertensions where t who has to be qualified The quantitative concept tends to lump all p imary hypertensions into one which is somewhat defeating The mosaic theory recognizes that hypertensions may be different at the start but has given some the impression th t by the time the condition is recognizable there are so many powerful secondary overlays that t would be useless to try to sort out a primary d turbance.

Actually this sorting goes on all the time Some 10 to 15 per cent of hypertension that p mary until 1940 is now secondary al o per cent of the primary hypertension of 1950 is now attributed to renal arterial stenos O basis of a series of serial renal angiog m trating epidemiologic expedient—it ha b gested that common anatomic having two renal arteries pred po sion in some people Actually the p renal arterial ...

demiologic terms except as these are primarily genetic. However, as suggested above, the muscle response may be in part a response to salt, and if so there should be some way to get at it. It may be that a plausible "therapeutic test" may be developed. For example, there is a small proportion of hypertensive patients who seem to respond very well to small doses of hydralazine, a myotropic and amine-releasing drug, and this fact may have a special meaning, as probably does the response to thiazide.

To close, it seems possible that a very few etiologically distinct mod lities include the majority of cases of primary hypertension. Mechanisms overlap as the process continues until pathogenesis becomes very complicated and perhaps inaccessible. Still, in the incipient phases it would seem possible to apply epidemiologic methods to separation of major groups in what now passes for "primary hypertension." This requires time and imagination, the development of reasonably specific and adequately practical techniques, and the conviction that such an analysis of the problem may further sort out the field of "primary hypertension" into subgroups that, once recognized, can sooner or later be understood.

A. C. Corcoran, M.D., C.M.
Department of Clinical Investigation
St. Vincent Charity Hospital
2222 Central Ave.
Cleveland, Ohio 44115

*Formerly Special Research Fellow, National Heart Institute, National Institutes of Health (HF 13 190); Presently Chief, Hypertension Research, V. A. Hospital, Ann Arbor, Mich. 48105.

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Cardiovascular findings in healthy children

In healthy children there is frequently a rather sharp pulse, a systolic murmur, and a loud third heart sound, and separate splitting of the second sound is usually even more obvious than in adults. It is important to know the normal range of these physical signs in order to diagnose the abnormal and in order to prevent unnecessary invalidism, as has happened in the past when the combination of fever and a systolic murmur sometimes resulted in a diagnosis of rheumatic carditis.

In children, electromechanical intervals and isoelectric times are shorter than in the adult, and more rapid contraction of the heart may at least partly account for the sharp pulse, rapid ejection and thus a systolic murmur, and rapid ventricular filling may explain the loud third sound. A thin chest wall may be another factor in increasing audibility of the normal sounds and murmurs.

The physiologic ejection systolic murmur so often heard in children is Grade 2 or 3 (of 6) in intensity, often grunting in quality, widespread in distribution, but usually maximal internal to the apex and in the pulmonary area, and soft in the aortic area. It is short, finishing well before both components of the second sound, and is probably due to rapid ejection into both the aorta

classified as questionably peaked By contra t in a group of 93 normal individual who were being followed in the Framingham Heart Survey and who were closely matched by age and sex with the 67 patients described above none showed a short Q T interval 4 (4.3 per cent) exhibited an elevated RS-T segment and 8 (8 6 per cent) had sharp T waves. In one the T wa was considered to be borderline. Thus it appears that it was only the sharpness of the T waves that might be a possible electrocardiographic clue to alcoholism

This observation is not new. It is true that Eliaser and Giansiracusa Berthood and Gollschlab and Frederiksen and Hed made no mention of such changes in their electrocardiographic studies of chronic alcoholism But Benchimol alone and with Schlesinger described tall and peaked T waves during the state of clinical improvement from beriberi heart disease that occurred among heavy drinkers of low grade alcoholic beverages in Brazil Furthermore the senior author of the present communication described a brisk electrocardiogram in chronic alcoholism in the chapter on electrocardiography in the last edition of S A Levine *Clinical Heart Disease* And finally Evans described what he considered to be distinctive electrocardiographic changes in 17 of 70 patients with so-called alcoholic cardiomyopathy These consisted of depressed dimpled T waves in 8 patients upright cloven T waves in 7 and spinous T waves of normal amplitude in E ans stated that he had not observed this particular type of spinous T wave in patients with myocardial injury from coronary artery disease

This appearance is not limited to alcoholic It may be seen as a normal variation among individual without heart disease It has been referred to by some as early repolarization It may be seen in the early stages of potassium intoxication Except that the R wave was tall in only of these patients it resembles the diastolic overloading of the left ventricle described by Cabrera This appearance has been ascribed by many workers to vagotonia by some to amphotonia and by a few who find the data to be contradictory to vegetative dystonia but the concept of a neuroregulatory type of electrocardiogram has never really taken hold in this country It is in fact not known whether the changes here described are the result of constitutional or nervous influences of changes in electrolyte balance or suggested by E ans of anatomic changes in the heart We have not addressed ourselves to this problem The following experience illustrates how the recognition of these changes led to a correct diagnosis

A 51 year-old housewife whose husband had died of an acute myocardial infarct during the preceding year complained of transitory pleuritic pain in the left side of the chest To the usual routine question she denied alcoholism She was requestioned on this point when after an interview and examination the electrocardiogram shown in Fig 1 B was recorded And thereafter even in the confessional atmosphere of the fluoroscopy room she admitted to no more than an occasional social drink But conversation with her family physician that evening revealed that the patient was actually a confirmed spree drinker who had spent much time in a well known suburban hospital that was devoted to the care of chronic alcoholics This experience parallel that of E ans who commented that information in regard to the alcohol intake of

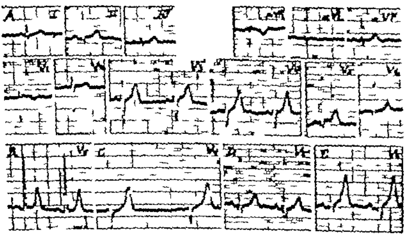


Fig. 1 Brisk electrocardiogram observed in chronic alcoholism 1 Twelve lead tracing 40 year old man with gynecomastia and peripheral neuropathy A battery of liver function tests was normal B E Precordial leads in a reluctant (see text) 1 mer (B) 44 year-old psychopath with vagotonia who had bled from a duodenal ulcer during the preceding year (C) a 47 year old obese and antagonistic man with angina pectoris (D) a convivial physician with essential tremor and peripheral neuropathy (F) The latter tracing corresponds to ... of the left ventricle Patients 1 B C and F had heart disease

of the fatty material found in the deeper layers of atheromatous plaques may be a secondary degenerative event. Recent fibrin-platelet thrombus is absent from the carotid arteries of patients who have not experienced recent transient attacks although the degree of stenosis may be unchanged. These findings are consistent with the view that the transient attacks are due to intermittent blockage of distal cerebral arteries with friable thrombus which quickly fragments when the circulation is restored. Experimental observations on emboli composed principally of platelets in the cerebral arteries of rabbits show that the platelets adhere tenaciously together at a site of arterial injury but once released as emboli they show a tendency to fragment.

Direct evidence for arterial embolism has come from ophthalmoscopic observations in patients with cerebral vascular disease. Rare cases of transient monocular blindness may show repeated passage of friable thrombus through the retinal vessels during attacks of blindness.[16] The behavior of these emboli is similar to experimental platelet emboli and in one case the presence of masses of agglutinated platelets was proved at autopsy. Not all retinal emboli behave in this way, and there are a number of reports of retinal arterial occlusion resulting from plugging of vessel with yellow crystalline material. These emboli may persist permanently or last for days or weeks. They have a bright scintillating appearance and are usually situated at arterial bifurcation in the region of the macula. They may produce initial symptoms consisting of altitudinal monocular hemianopia or nerve fiber defect scotomas or they may be symptomless. There may be retinal edema in the distribution of the occluded vessel with a number of soft exudates. Loss of vision is commonly transient but may be permanent. Recently, pathologic examination of a single case has shown that the emboli are composed of atheromatous material with a high proportion of cholesterol ester. The source of the emboli is commonly the carotid artery. Atheromatous retinal embolism is not uncommon event in patients with cerebral vascular disease, especially if they are diabetic or hypercholesterolemic. Similar emboli may impact in cerebral vessels. Carotid angiography by direct puncture and carotid endarterectomy may be followed by showers of small atheromatous emboli. Although atheromatous embolism has been recognized pathologically at other sites such as the kidney, the vulnerability of the brain and retina to ischemia makes clinical recognition of carotid emboli more likely.

R. Ross Russell, M.D.
Institute of Neurology
The National Hospital for Nervous Diseases
Queen Square
London, W.C. 1, England

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Letter to the Editor

Athens University School of Medicine
4 Skoufa Street
Athens 136, Greece
September 1, 1964

T the Editor

In the third paragraph of Dr. H. W t on paper Intrinsicoid Atrial I W e Deflections n *Unipolar Intracardia Electrogram* which ap peared in the *American Heart Journal* Volume 68 page 3 July 1964 it is tated that The term intrinsicoid ha been u ed becau the electrode although in ide the heart is not in on tact w th the myocardium nd these deflectio n are therefore not truly intrin ic.

As is known the term intrinsic deflection ntroduced by Lewi nd hi co tt ign l the arrival of the excitation process beneath the proxi mal contact of p ir of electrodes rr nged r dially with referen t the sinus node The tlogou deflection in pre ord l peripheral nd mo t of the intracord il le d called intrinsicoid

Although there is no objecti n t the above mentioned conve t onal term eve though I would personally prefe to ll the intrin i nd extrin ic deflection *autochthonous* nd *heterochthonous* from a this or a other a ther r ground or plu I think that in the title as well as the text f Dr W tson paper the term l trogr m i sed ncorre tly ll the urve pre sente l bei g k troc rdiograms rather than lec tr g n

I leed n s ra ng Samojloff work ng n the l w found th t its form in the curve re corde l th lead dire tly on the heart (or on strips) differe l f th the curve taken w th indirect lead he theref troduced the term electro gram nd l t rdiogram to d tinguish between re rd tak n w th direct leads and those obtained with l rect lead Thi terminology has ever since l l pt d by all those wh have been engaged w th th k trophysiology of the heart

Thus it k t that the term electrogram and/or n l electrography as used by Dr Watson nd Dr Emslie-Smith are inadm ssible and the rr t (nd not confu n) term nology is that u ed by other investigators is for example Levine an l sso tes Testelli Dickerson and C rn n l Battro an l Bidoggia to mention only those li ted in the ref rences of Dr Watson s p pe

Konstantine S Zakopoulos M D
A istant P ofessor of P thological Physiology
Athens University School of Medicine
a l Cardiov scula Laboratory
Sotiri T B Sanatorium and Hospital for Chest Diseases

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Book reviews

THE YEAR BOOK OF CARDIOVASCULAR AND RENAL DISEASES (1963 1964 Series). Edited by W. I ector Harvey M D John W. Kirklin M D Alexander S Nadas M D Oglesby Paul M D Victor E. Pollak M D T Joseph Reeves M D Robert W. Wilkins M D and Irving S Wright M D Chicago 1964 Year Book Medical Publishers Inc. 541 pages Price $10

This 1963-1964 series of the Year Book is valuable to the field of cardiovascular and renal disease. The book con ts of course of summaries of fairly recent pape s selected by the editors A in any book of thi sort the summarie unfortu nately reflect the editorialized presentation of those who select and condense the original papers The reader mu t be aware of this and should realize that many equally and even more im portant papers are not included and that even those summarized do not do full justice to the original papers Nevertheles th a u eful book for those who d not follow the literature closely

HEART AND SPORT By Erne t Jokl M D Univer sity of Kentucky Lexington Ky Publ No 5 1 in the American Lecture Series Springfield Ill Charles C Thomas 117 pages Price $6

In this monograph the author ttempt to define (the) natur and scope of appl ed cardi vascular physiology of exercise to summarize a number of recent ad ances of epidemiology and to pla int perspective selected clinical and path logical find ngs

In dealing with the cardiovascular phy logy of exercise the author collects many tudies n different parameter (hea t rate heart ize st ok volume etc) in a gr up of superbl trained th letes These observ tion are contra ted to the findings in normal subjects to those reco ded in less completely trained pe sonnel For phy cians accustomed t l ok in at diseased card s vascular system the observ t n present startling contra t This hand served with physical condit o ng ex trikin but unfor tunately m most ses th se obse tion are derived from ers ndirec t meas ures and thu can giv only gene l t end

The epidemi l d ta ummarize tudies on the longevit f thle nd vers as well to collect the s d l le series cerning the n dence of o on rtery l ease edentary opposed to ph ll r perple Each tudy carefully ef 3 nd the a ailabil ty of data trongly support the idea that ta ned phy cal activit soc ted with d rea ed inc den e of coronary tu d sea

Other t pic dealt w th are udd n de th in athletes n oc d l h pert ph infarct n in athletes an l th phy logy of the response f the body t xc se

The tex l aw t deal w th the perf rman e of l scard l rdio scular tem l tt t a guide for counseling cardiac patient w th regard to participation in physical activity It i a look at a very special segment of the population and is filled with interesting observations on and a pleasant presentation f the statistical evidence bearing on daily level of activity and the inci dence of coronary artery disease

FRONTIERS IN ANGIOGRAPHY Compiled and edited by Manuel Viamonte Jr M D A sociate Professor of Radiology University of Miami and Raymond E Parks M D Professor and Chairman of Radi ology Univer ty of Miami Springfield Ill 1964 Charles C Thomas Publisher 56 pages Price $19 50

This book cons ts of a group of chapters written by many contributors some of whom have devoted a great deal of effort to the problem of angiography both in the laboratory and in the clinic and other of wh m have had relatively little experience w th it other than that en countered at any cardiovascular center The ubject discu sed include angi graph in n genital defects coronary ngiographs pulmo nary angiography angiography applied t the detection of tumors peripheral ascular angiog raphy and cerebrovascular angiography There are good discus ions of techniques as well as excellent illustrations of roentgenograms There are panel type di cus ons at the end of each chapter These mposia and the entire book is based upon refresher ourse on Ad ances Ang ography presented in Miami on March 21 through 23 1963

This book is ecommended to beginners n cardiology internists rad ol gi ts and tudents s a supplement to other and more pecific pub lications

AN INTRODUCTION TO ELECTROCARDIOGRAPHY By Thomas M Blake M D A sociate Professor f Medicine University of M ssissippi School of Medi ne New York 1964 Appleton Century Cr fts Di ion of Meredith Publishing C mpany 143 pages Price $4 9

This is a small paperback book on electr card og raphy fo beg nners especially direc ted t third ear med cal stud nts A the autho tates there are many book on the subject and each autho has his own approach to the p esent t of the subject of electrocardiograph Dr Blake is based upon the experience of h w teach ng The p esentation is brief and at times the dis cuss ons are too brief For example toda n ant justif ed to d miss the U w th parag raph to w t The U wa should be mentioned for the sake of completeness Frequently a mall deflection f llow the T wave an l is referred to as the U wa Attention is rarel paid to it be cau e it gnif cance poorly und rstood probably is related n some way to repo

tion. The important role of the I w e in the diagnosis of electrolyte imb l nce nd i chemic heart disease is well known.

The lack of an adequate number of illustr tions so important to beginners who h ve s much difficulty visualizing a description f electrocardiographic patterns is a parti ular! sig nificant weakne s of the book. Thi s ll em phasized by the author on page 13 in a description of the elephant by blind men. Y t on page 67 in a few lines he describes atrial fibrillat n nd presents no illustration of typical tracing.

This short book presents Dr. Blake s approach to the teaching of electrocardiography to third year medical students. Those who are interested in his method should thumb through the book first t learn whether it i worth the pri e nd satisfies their need. They may be disappointed if the make the purchase ht unseen.

Announcements

OPERABLE HEART DISEASE the Se th Annual Conference under the u pices of the C tinuing Educ tion Committee of the Presbyterian Medical Center, San Francisco, Calif., will t ke place on March 6 and 1966.

For information write t Dr. Frank Gerbode, Conference Chairman, Presbyterian Medical Cen r, Cl y and Webster Street, San Fran isc 15, Calif.

The following dates for the TENTH CONGRESS OF THE PAN PACIFIC SURGICAL ASSOCIATION have been announced: Part I—September 20-28, 1966, in Honolulu, Hawaii; Second Mobile Educational Seminar—Part II, September 28 through October 10, 1966, in Japan and Hong Kong; and Part III, September 28 through November 1, 1966, in Japan, Hong Kong, the Philippines, Thailand, India, Singapore, Australia, and New Zealand.

For further information write to the P n P cific Surgical A s ci n R m 236, Alexander Young Bld., Honolulu, Hawaii 96813.

The Daniel Freeman Hospital and the Los Angeles County Heart A ciation will co-sponsor a Seventh ourse n ADVANCED ELECTROCARDIOGRAPHY AND VECTORCARDIOGRAPHY to be given from March 13 through March 19, 1966. The princip l peakers will be Arthur Grishman, M.D., of New York City, and Demetrio Sodi-Pallares, M.D., of Mexico City. This program is designed for the experienced electrocardiographer. The registration fee: $50.

Inquiries should be directed to Walter S. Graf, M.D., Program Chairman, The Daniel Freeman Hospital, 333 North Prairie Ave., Inglewood, Calif.

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Editorial

Clinical interpretation of electrocardiogram by means of electronic computers

*Harold D. Levine, M.D.**
Boston, Mass.

The interpretation of electrocardiograms on a large scale can be a fatiguing, arduous, and onerous task, consuming seemingly endless man hours. Variations occur from observer to observer and in the same reader from time to time in the ease and accuracy of reading.[1,2] With the advent of the electronic computer, we are now provided with a means of measuring, calculating, and interpreting various phenomena with a speed, accuracy, and consistency impossible by man. It was hardly necessary to seek out possible applications of this technique in the biomedical sciences, the electrocardiogram, presenting an objective and easily measured time course and amplitude pattern, virtually suggests itself. Beginnings are already being made in the elaboration of programs for the recognition of abnormal patients among a largely normal population.[3] Here the electrocardiogram under study is compared with a composite normal. The task of sorting out within a largely abnormal hospital population different types and degrees of abnormality will be much more difficult. Here the tracing being studied must be compared not only with the spectrum of normality but also with the patient's own tracing of the previous day, week, month, or year.

Certain mechanical problems will have to be overcome. This includes erratic or even consistent drift of the base line, suprathreshold noise from alternating current interference, muscle tremor, the vibration of air conditioning apparatus, and the like. Precise standardization of the curves will be imperative. The very identification of the various components of the electrocardiogram may pose a problem. A decision will have to be reached of whether the method of Caceres[4] for determining a point of reference for the identification of the QRS complex is valid and reliable. In this technique the maximum negative amplitude of the first derivative of the electrocardiogram is used in identifying the QRS complex and thus its constituent Q, R, and S waves, and thence the other components of the electrocardiogram, the P, T, and U waves. The P and T waves will generally be differentiated one from the other by the fact that, although each is a low frequency curve, the P wave precedes the QRS complex and is of relatively short duration, whereas the T wave follows the QRS complex and is of relatively long duration. But confusion may be introduced by a very rapidly changing potential in the P wave over the right precordium in the pres

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*Address: [illegible] Laboratory [illegible] Hospital, 721 H[illegible] Ave., Boston [illegible]

ence of atrial enlargement (large atrial in trinsicoid deflection) or in the T wave in precordial leads in the case of potassium intoxication either of which could be sensed by *the machine as the point of reference for* the QRS complex The machine could also be confused if the T and P waves are super imposed

The U wave is a difficult enough problem for the unaided electrocardiographer It is not always easy to tell whether the hump on the latter part of a T wave is a super imposed P wave a U wave or the second notch of a bifid T wave The U wave may differ only very slightly from the P wave Therefore a U wave could be confused with the nonconducted P wave of an atrial pre mature beat or of second-degree (2 1) atrioventricular heart block For the same reason the measurement of the Q T inter val will be as difficult for the machine as it is for man Whether it is feasible or neces sary to differentiate the U wave from the P wave by direct confrontation of duration amplitude or slope remains to be deter mined

In current practice the clinical electro cardiographer employs at least 12 leads Data of such volume would certainly over the memory units of the computer vergent approaches have already become apparent in the effort to reduce the quan tity of input data In a pilot study of feasi bility Caceres has empirically measured the amplitude and duration of the P Q R S and T waves the amplitude of the RS T segment in its early mid and late portions the amplitude of the U wave and the dura tion of the P Q S T Q T and R R inter vals in Leads II and V_1 In this technique the amplitude of the T wave for example in one lead is compared empirically with a normal range of amplitudes

The study of the T wave through the determination of the ventricular gradient as proposed by Wilson has been hindered by certain practical considerations The manual determination of the gradient is too tedious and time consuming and until recently it has been possible to study the gradient only in the frontal plane Pip berger[10,11] however has pointed out that by the use of a corrected orthogonal three lead system in which each of the three leads x y and z can be accorded a similar strength it is possible to determine a *spa tial* QRS and T wave axis and a *spatial* ven tricular gradient Pipberger[1] believes that these three leads yield the same clinical *information as the conventional 12 lead* electrocardiogram If this more sophisti cated technique proves to be practical the temptation will be to include in the routine reading of the electrocardiogram by the computer other calculations not always made in the routine reading As examples the frontal plane electrical axis the rate corrected Q T interval Grant's angle (the angular deviation between the first and the last 0 04 second QRS vector) or as sug gested by Pipberger polar vectors eigen vectors and the spatial magnitude orien tation and velocity could be determined and printed out with each interpretation

It has become abundantly clear to work ers in this new field as it has been to clinical electrocardiographers in the past that no matter how resolute the original determina tion to proceed on a purely orderly and logical basis in the interpretation of trac ings there is an inevitable and involuntary tendency to empirical reading Thus even with such possibilities as are presented by the computer there may be a distinct trend to substitute pattern recognition[12] or confrontation techniques for sequential yes no logic The difficulties inherent in pro gramming the arrhythmias have been al luded to but no publications have yet ap peared on this aspect of electrocardio graphic data processing Most of the opti mism on the future of this approach in electrocardiography has been expressed by electrical and computer engineers not by physicians By and large electrocardiogra phers perhaps because of their own un familiarity with this field have been shamed into silent acquiescence and have had precious little to say on the subject But it has yet to be proved that clinical electrocardiography—as distinct from elec trocardiographic surveying—is better per formed by machine methods than by human brain power The question whether the ma chine can actually be programmed to differ entiate inconsequential minutiae from sub tle changes of possible significance and to do this as well—or as poorly—as we can awaits the accumulation of a large body of solid experience with the technique And

we must bear in mind that in that first showdown on the feasibility of steam locomotion the horse defeated the Tom Thumb

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Clinical communications

Peri-infarction block
Postmyocardial infarction intraventricular conduction disturbance

*Robert A. Corne, M.D.**
*Thomas W. Parkin, M.D.***
*Robert O. Brandenburg, M.D.**
*Arnold L. Brown, Jr., M.D.****
Rochester, Minn.

First and associates[1] introduced the term "peri-infarction block" to refer to a conduction disturbance due to infarction of the subendocardial region of the myocardium and characterized by (1) evidence of myocardial infarction of the subendocardial region of the ventricular wall or of transmural infarction with a circumferential region of subendocardial damage, (2) QRS complexes in the limb leads that are 0.11 second in duration or exceed it, and (3) a characteristic QRS pattern in the unipolar precordial and extremity leads. Grant[2,3] elaborated on the concept of peri-infarction block, emphasizing that a conduction defect may be present without prolongation of the QRS interval. Accordingly, he stated[3] that the basic features of peri-infarction block are an abnormality of the direction of the initial forces of the QRS interval of a type characteristic of myocardial infarction and an abnormality of the direction of the last forces of the *QRS interval so that they* point opposite to the initial QRS forces, with little or no prolongation of the QRS interval. The hallmark of peri-infarction block, therefore, is the wide angle between the mean vector for the initial 0.04 second of the QRS interval and the mean vector for the last 0.04 second of the QRS interval.[4] Davies and Evans[5] pointed out that when the S_1-S_3 pattern is present the initial and terminal vectors may be widely separated in the fashion of anterolateral peri-infarction block without the mean vector for the first 0.04 second being farther to the right than +90 degrees; they contended that a Q wave less than 0.04 second in duration in the presence of the S_1-S_3 pattern can signify anterolateral infarction.

The present study was undertaken in order to determine whether an abnormal direction of the mean initial 0.04 second QRS vector of a type characteristic of infarction was an essential component of this type of postmyocardial infarction intraventricular conduction disturbance.

Composition of study

In a recent study[7] of 96 adult patients, there were cardiac pathologic find-

From the Mayo Clinic and Mayo Foundation, Rochester, Minn.
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*Fellow in Cardiology.
**Section of Medicine.
***Section of Experimental and Anatomic Pathology.

ings in 86 These cases represented (1) aortic valve stenosis (37 cases) (2) left ventricular hypertrophy without significant coronary sclerosis infarction or valvular disease (21 cases) and (3) coronary sclerosis without myocardial infarction or valvular disease (28 cases) Of these 86 there were 21 cases in which the angle between the mean initial 0 04 second and the mean terminal 0 04 second QRS vectors was 110 degrees or greater and in which there were no Q waves of 0 04 second duration in the standard limb leads The following is a report of the cardiac pathology in these 21 cases

Methods

The interventricular septum and the walls of the left ventricle were examined grossly and microscopically in each case to determine the presence location and extent of fibrosis

Sections for microscopic study were taken at four levels from the anterior portion of the interventricular septum and at five levels from the anterior and from the lateral walls of the left ventricle beginning at the base and proceeding to the apex

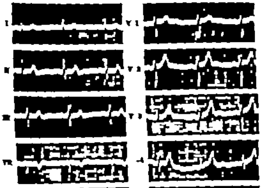


Fig 1 ECG of 58 year-old man Angle between mean initial 0 04 second and mean terminal 0 04 second QRS vectors is 148 degrees $\hat{A}_{QRS}$ is +30 degrees At necropsy the heart weight was 260 gram and there was moderate coronary atherosclerosis no myocardial infarction and minimal microscopic fibrosis

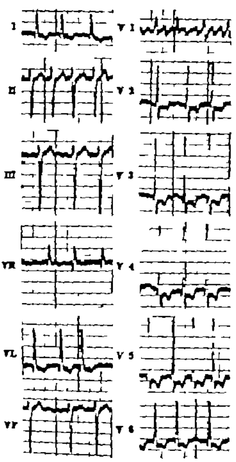


Fig 2 ECG of 77 year-old man Angle between mean initial 0 04-second and mean terminal 0 04-second QRS vectors is 134 degrees $\hat{A}_{QRS}$ is −68 degrees At necropsy the heart weight was 3 5 grams and there was moderate to-marked coronary atherosclerosis no myocardial infarction and moderate to-marked microscopic myocardial fibrosis

The microscopic sections were approximately 4 square centimeters in area The sections were prepared with hematoxylin and eosin and the Mallory Heidenhain stains Areas of recent infarction or fibrosis were considered to be extensive if they involved more than one half of the section Smaller lesions were referred to as focal and were subdivided at a magnification of 100 times as follows minimal if they involved less than one fourth of the field moderate between one quarter and three quarters of the field and marked greater than three quarters The location in the subendocardial intramural or subepicardial regions was recorded

The electrocardiographic tracings in the present series included both the 6 lead electrocardiogram (Standard Leads I II and III and Precordial Leads V_1 V_4 and V_6) and the 12 lead electrocardiogram The mean manifest QRS axis in the frontal plane and the mean initial 0 04 second and mean terminal 0 04 second* QRS vectors were plotted on the hexaxial reference system The method used was a modification of that of Ashman and Byer[8] with reference to the recommendations of the Committee on Electrocardiography of the American Heart Association[9] The net area enclosed by the QRS complex as well as that area enclosed during the initial 0 04 second and the terminal 0 04 second of the QRS interval in Leads I and III was determined in each case by algebraic summation of the value obtained by multiplying the amplitude by one half the duration at the base These were expressed in Ashman units The level of reference for an upward QRS deflection was the upper edge of the trace at the beginning of the QRS interval whereas that for a downward QRS deflection was the lower edge of the trace at the beginning of the QRS interval

Results

There were 21 cases in which the angle between the mean initial and the mean terminal of 0 04 second QRS vectors was 110 degrees or greater and in which there were no Q waves of 0 04 second duration in the limb leads (Table I) Ten of the 21 cases with this wide angle also had left axis deviation of $\hat{A}_{QRS}$ beyond −30 degrees No evidence of myocardial infarction on gross examination was present in 9 of these 10 cases in one there was infarction of the anterior portion of the interventricular septum and the anterior wall of the left ventricle Moderate to marked fibrosis as determined by microscopic examination was present in 8 cases in this category The fibrosis was diffuse involving the anterior portion of the interventricular septum and the anterior and anterolateral walls of the left ventricle In 5 cases there was marked left ventricular hypertrophy* Neither gross evidence of myocardial infarction nor microscopic evidence of moderate to marked fibrosis was noted in the 11 cases with the wide angle without left axis deviation Marked left ventricular hypertrophy was present in 5 of these patients

In 14 of the 21 cases with this wide angle between the mean initial and terminal 0 04 second QRS vectors but without Q waves of 0 04 second duration in the limb leads the duration of the QRS interval was within normal limits Six of the 14 cases also had left axis deviation of $\hat{A}_{QRS}$ beyond −30 degrees No gross evidence of myocardial infarction was present in these cases Microscopically moderate to marked fibrosis was present in 4 of the 6 cases Neither gross evidence of myocardial infarction nor microscopic evidence of moderate to marked fibrosis was noted in the 8 cases with the wide angle but without left axis deviation and without prolongation of the QRS interval

Discussion

In the present study myocardial infarction was present in only one of 10 cases in which there was an angle of 110 degrees or greater between the mean initial and the mean terminal 0 04 second QRS vectors and with left axis deviation of $\hat{A}_{QRS}$ beyond −30 degrees but without Q waves of 0 04 second duration in the limb leads This infarct involved the anterior portion of the interventricular septum and the anterior wall of the left ventricle Neither infarction nor microscopic evidence of moderate to marked fibrosis in the anterolateral region of the left ventricle was present in any of 11 cases with a wide angle without diagnostic Q waves and without left axis deviation (Fig 1) Thus the presence of a wide angle between the mean initial and terminal 0 04 second QRS vectors in the absence of other electrocardiographic abnormalities did not aid in the diagnosis of myocardial infarction The addition of left axis deviation of $\hat{A}_{QRS}$ beyond −30 degrees to the above mentioned pattern suggests microscopic

*In those instances in which the total QRS duration was less than 0 08 second the mean vector of the terminal part of the QRS interval remaining after the initial 0 04 second was plotted

*Marked left ventricular hypertrophy [illegible] heart weight greater than 175 per cent of the expected heart weight on the basis of [illegible] and body weight[10]

Table I Summary of electrocardiographic and pathologic findings

Group	Number of cases	Pathologic findings (number of cases)		
		Infarction	*Moderate to marked microscopic fibrosis*	*Marked left ventricular hypertrophy*
Wide angle but without Q waves†	21	1	8	10
With LAD	10	1	8	5
Without LAD	11	0	0	5

Marked left ventricular hypertrophy refers to heart weight exceeding 1 5 per cent of the maximum expected heart weight on the basis of age and body weight[10]

† Angle of 110 degrees or greater between the mean initial 0 04-second and the mean terminal 0 04-second QRS vectors, without Q waves of 0.04-second duration in the standard limb leads.

Left axis deviation of Âqrs beyond −30 degrees.

myocardial fibrosis[7] (Fig 2) Hence an abnormality of the direction of the mean initial 0 04 second vector of a type characteristic of infarction is an integral part of this postmyocardial infarction intraventricular conduction disturbance It is suggested therefore that the term peri infarction block be restricted to the combination of abnormalities of the terminal QRS forces with the initial QRS deformity characteristic of infarction as originally proposed by Grant[4] Marked left ventricular hypertrophy was present in 10 of the 21 cases with a wide angle but without Q waves of 0 04 second duration Only one patient in this study had pulmonary emphysema and in this case the angle between the mean initial and terminal 0 04-second QRS vectors was 150 degrees

Summary

The cardiac pathology is reported in 21 adult patients in whom the angle between the mean initial and mean terminal 0 04 second QRS vectors was greater than 110 degrees but in whom there were no Q waves of 0 04 second duration in the standard limb leads In only one case was myocardial infarction present It is suggested therefore that the term peri infarction block be restricted to the combination of abnormalities of the terminal QRS forces with the initial QRS deformity characteristic of infarction

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Effect of concentrated contrast media during angiography on plasma volume and plasma osmolality

Lloyd L. Iseri, M.D.
Martin A. Kaplan, M.D.
Michael J. Evans, B.A.
Eldon D. Nickel, M.D.
Downey, Calif.

Recent interest in radiologic visualization of the heart, aorta, and its major branches has led to the use of large volumes of highly concentrated radiopaque material. Among the complications which have occasionally been encountered in these studies are acute pulmonary edema,[1] acute cardiac arrhythmias,[2,3] and unexplained cardiovascular deaths.[4]

The present study was instituted to determine the effect of concentrated hyperosmotic radiopaque material on the plasma volume and plasma constituents, since it appeared to be reasonable to expect that a sudden rise in plasma osmolality after injection of the opaque material might produce changes in the plasma.

Method

Eight retrograde aortographic studies and one venographic study were done on 8 patients using 30 to 40 milliliters of 75 per cent sodium and methylglucamine diatrizoate solution.† Two of the 8 patients received two separate injections and one received three, with 30 to 45 minutes of rest between injections.

Twenty to 30 microcuries of radioiodinated serum albumin were first injected into the patients, and after at least 30 minutes of equilibration, three 10 minute samples of blood were drawn in order to obtain control levels of plasma I^{131}, plasma chloride, plasma osmolality, and blood hematocrit. The opaque solution was then power injected through the catheter for aortographic and venographic studies, and a series of samples of arterial blood was again drawn at 2, 5, 10, and 30 minutes after the injection. Electrocardiographic tracings and direct arterial blood pressures were monitored throughout the study, and records were obtained at frequent intervals. Control plasma volumes were calculated by extrapolation of three control isotope counts back to zero time. All subsequent plasma volumes were determined by comparing the observed isotope count to the predicted isotope count. Determinations of blood hematocrit, plasma osmolality, and plasma I^{131} activity were made according to previously described methods.[6] Plasma chloride was determined by the method of Schales and Schales.[7]

From Medical Services and Radiology [illegible] Los Angeles [illegible] Downey, Calif., and the Department of Internal Medicine, [illegible] Los Angeles, Calif.
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Address: Medical Services [illegible] Los Angeles [illegible] Downey, Calif.
†Hypaque M 75 per cent, Winthrop Laboratories, New York, N. Y.

Results

The results of the effect of injection of concentrated diatrizoate solution into the vascular channels are summarized in Table I and Fig 1 and illustrated in Fig 2 A sudden increase in plasma volume was observed in all the patients averaging 215 ml at 2 minutes after injection The increase amounted to 170 ml at 5 minutes and 84 ml at 10 minutes after injection At 30 minutes there was a tendency for the plasma volume to be less than that of the control period (−41 ml) In 2 patients who were followed for 45 minutes the plasma volume declined still further averaging 190 ml less than the control

Blood hematocrit decreased an average of 2 16 ml per cent in 2 minutes 1 98 ml per cent in 5 minutes 1 35 ml per cent in 10 minutes and 0 28 ml per cent in 30 minutes

Plasma osmolality rose consistently with an average increase of 5 9 mOsm per liter in 2 minutes 3 7 mOsm per liter in 5 minutes 2 3 mOsm per liter in 10 minutes and 0 2 mOsm per liter in 30 minutes

Plasma chloride was somewhat erratic but decreased in 7 of 8 cases The average change was −4 4 mEq per liter at 2 minutes −3 1 mEq per liter at 5 minutes −3 5 mEq per liter at 10 minutes and −2 8 mEq per liter at 30 minutes

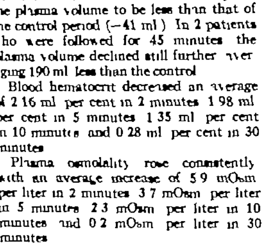


Fig 1 Effect of injection of 75 per cent Hypaque-M on the plasma volume plasma osmolality and blood hematocrit The dark line represents the mean change and the shaded area represents standard deviation of n ... topographic studies

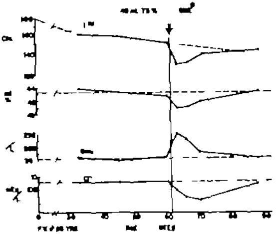


Fig 2 Effect of 10 ml of 75 per cent Hypaque M on plasma I[131] (RISA) blood hematocrit plasma osmolality and plasma chloride

Blood pressure invariably rose 2 minutes after the injection of the radiopaque material and tended to remain elevated for over 10 minutes

No untoward reactions were observed although in one patient (Case No 7) the blood pressure rose to alarming heights from 130/75 to 295/135 mm Hg 10 minutes after injection Repeated multiple injections of concentrated radiopaque material caused similar changes in plasma volume and blood hematocrit (Fig 3) A subsequent decrease in plasma volume 30 minutes after second injections appeared to be more marked than after single or the first injections

Discussion

It is apparent from these studies that concentrated radiopaque material injected into the blood stream rapidly causes a transient expansion of the plasma volume amounting to as much as 500 ml at the end of 2 minutes The magnitude of increase was 2 9 per cent to 14 3 per cent with mean of 8 2 per cent of the initial volume Within 5 minutes the plasma volume begins to decrease and after 30 minutes the volume tends to fall below the control levels

The initial increase in plasma volume was undoubtedly due primarily to the osmotic effect of the radiopaque material Osmolar concentration of this substance was found to be as high as 2 000 mOsm

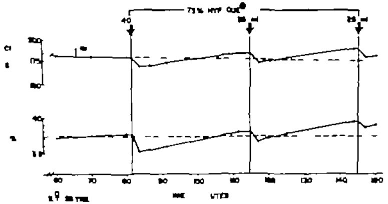


Fig 3 Effect of multiple injections of 75 per cent Hypaque M on plasma I[131] (RISA) and blood hematocrit

per liter and the mean increase in total plasma osmolar content (78 mOsm) was approximately equal to the mean osmolar quantity (73 mOsm) of the material injected into the patients Furthermore a direct linear relationship was demonstrated at 2 minutes after injection between the per cent increase in plasma volume and the increase in plasma osmolality (Fig 4) As might be predicted the increase in plasma volume during the first 2 minutes was due mostly to migration of water from the cells into the plasma compartment as evidenced by a fall in plasma chloride concentration and the relatively stable mean total plasma chloride content (301 mEq for the 8 cases during the control period and 311 mEq for the same cases at 2 minutes)

Not all of the initial increase in plasma volume could be related to the osmolar effect of the hypertonic radiopaque material Analysis of individual cases revealed an increase in total plasma osmolar content over and above the amount ascribable to the injected material in 3 of the patients (Cases 5a 5b and 8) In 2 of these patients (Cases 5b and 8) significant increases in total plasma chloride content were found indicating either an influx of interstitial fluid carrying chloride ions or an outpouring of fluid and chloride ions from the red blood cells These changes could conceivably result either from transient disturbances of acid base balance brought about by injection of a material which generally has a pH of approximately 6 5 to 7 5 or from indirect action of the contrast media on plasma albumin and red blood cells[8 9]

After the initial expansion of the plasma volume there was a rapid movement of fluid out of the vascular compartment Mean total plasma osmolar content fell although again the total chloride content remained fairly stable until the thirtieth minute when it too fell Although urinary output was not followed many of the patients expressed their desire to urinate and it was apparent from fluoroscopic observation of the distended urinary bladder filled with opaque material that osmotic diuresis had been induced by the concentrated solution

Just how these changes might cause a

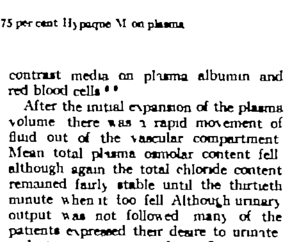


Fig 4 Correlation between increase in plasma volume and increase plasma osmolality 2 minute after the injection of 75 per cent Hypaque M ($p < 001$)

Table I Effect of 75 per cent diatrizoate solution on plasma volume blood hematocrit plasma osmolality plasma chloride and blood pressure

Case	Age (yr) Sex Surface area (M²) Amount injected (ml) Site injected	Time after injection (min)	Plasma volume (ml)	Blood hematocrit (ml %)	Plasma osmolality (mOsm/L)	Plasma chloride (mEq/L)	Blood pressure (mm Hg)
1	53 F	0	3 033	37 3	270	109 5	195/100
	1 69	2	3 210	35 1	274	106 3	205/103
	40	5	3 19[illegible]	35 4	27[illegible]	110 7	215/100
	Ao arch	10	3 127	36 0	272	108 0	217/105
		30	2 927	37 9	268	108 0	
2	34 F	0	2 006	48 3	287	109 5	155/104
	1 50	2	2 218	45 5	295	108 9	180/105
	40	5	2 163	45 8	291	110 7	164/94
	Ao arch	10	2 176	46 7	291	101 9	153/95
		30	2 006	47 0	288	106 3	
3	59 F	0	2 757	40 7	297	10[illegible] 3	226/108
	1 90	2	2 857	39 0	301	101 9	231/112
	30	5	2 853	39 5	299	103 6	
	Abd ao	10	2 798	39 7	299	104 5	231/107
		30	2 757	40 4	297	103 6	224/108
4	58 F	0	2 178	44 [illegible]	285	119 7	133/90
	1 39	2	2 341	4[illegible] 9	29[illegible]	109 7	156/94
	30	5	2 297	43 2	291	109 7	158/95
	Abd ao	10	2 270	43 8	288	114 9	155/95
		30	2 203	44 1	288	114 0	154/87
5a	53 M	0	2 641	41 3	295	109 4	127/76
	1 78	2	2 934	39 7	30[illegible]	99 2	15[illegible]/90
	30	5	2 794	39 8	297	100 0	166/94
	Subclav v	10	2 797	40 4	295	99 1	168/98
		30	2 72[illegible]	41 7	293	107 1	170/99
5b	53 M	0	2 726	43 3	285	106 7	145/98
	1 78	2	3 116	40 8	292	101 8	165/105
	40	5	2 994	41 0	290	96 5	165/105
	Ascend ao	10	2 812	41 8	286	94 7	162/102
		30	2 639	43 4	284	105 3	165/105
6	50 M	0	3 652	38 2	288	116 0	150/93
	2 04	2	3 758	36 4	290	108 0	187/102
	40	5	3 755	36 4	289	105 5	187/102
	Ao arch	10	3 657	37 0	288	115 1	199/106
		30	3 509	36 8	287	109 2	
7	38 M	0	3 406	38 9	271	10	130/75
	1 77	5	3 610	36 4	277	114 0	
	40	10	3 595	38 0	276	108 8	295/135
	Ao arch	30	3 167	39 5	273		200/110
8	42 M	0	2 930	43 1	287	104 8	152/9[illegible]
	2 07	2	3 207	40 8	299	107 0	1 0 10
	40	10	3 008	41 0	284		166/99
	Abd ao	30	2 930	43 0	28[illegible]	101 8	
	Mean change	2	+215	−2 2	+6	−4 4	
		5	+170	− 0	+4	−3 1	
		10	+84	−1 4	+[illegible]	−1 5	
	(p = < 01)	30	−41	− 3	+ 2	−2 8	

[illegible]

deleterious effect on the circulation is difficult to assess. Sudden expansion of plasma volume immediately after injection of hyperosmotic solution could overdistend the heart and precipitate acute cardiac failure or initiate fatal arrhythmias. Direct osmotic effect of concentrated contrast medium on the myocardium during coronary angiography or during proximal aortography may interfere with myocardial contractility and produce dire results. Expansion of plasma volume coupled with the observed tendency of the small arterioles to constrict[1, 11] would raise the blood pressure. Such reactions would, of course, be hazardous in patients with aneurysms or with weakened vascular walls.

Delayed complications of retrograde aortography and angiocardiography might be due to subtle but profound changes in fluid and electrolyte balance brought on directly by osmotic dehydration of the cells or indirectly by continued osmotic diuresis. These complications would be expected to occur more frequently in labile infants[4] who are given relatively more radiopaque material than adults.

A recent paper published after completion of our studies stressed the importance of plasma hypertonicity after angiocardiography.[12] A rise in plasma osmolar concentration by itself, however, might not truly forecast the gravity of the situation, since the present study reveals that within 2 minutes after injection, water enters the vascular compartment and dilutes the plasma. The changes observed in this study would also explain the frequency of complications after multiple injections.[4, 13]

Summary

The effect of injection of hypertonic radiopaque solutions on the plasma volume, hematocrit, osmolality, and chloride levels was studied in 8 patients undergoing retrograde aortography and venography. A sudden increase in plasma volume with a concomitant rise in plasma osmolality and fall in blood hematocrit and plasma chloride concentration were observed. The changes were ascribed to the passage of cellular water into the plasma in response to a sudden elevation of plasma osmolality and the passage of interstitial fluid into the plasma in response to changes in acid-base balance. The subsequent decrease in plasma volume which tended to fall below the control volume was thought to be due primarily to osmotic diuresis produced by the hyperosmotic radiopaque solution. The relationship of these changes to certain complications of retrograde aortography and angiocardiography are discussed.

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Myocardial degeneration in cardiac sarcoidosis

Histochemical and electron microscopic studies

Victor J. Ferrans, M.D., Ph.D.
Richard G. Hibbs, Ph.D.
William C. Black, M.D.
John J. Walsh, M.D.
*George E. Burch, M.D.**
New Orleans, La.

Invasion of the myocardium by sarcoid granulomas with ensuing myocardial fibrosis has been considered to be responsible for the clinical manifestations of sarcoid heart disease.[1] The pathogenesis of the heart failure, however, is difficult to explain. In this report of the first electron microscopic and histochemical study of the heart in sarcoidosis, data are presented which suggest that the cardiac failure may be due to extensive myocardial damage that is not evident by the usual techniques of histopathology.

No claims are being made as to the specificity for sarcoidosis of any of the changes found, but a description of our observations is reported in the hope that similar studies will be undertaken by others.

Case report

J. M., a 25-year-old Negro man, was in good health until 3 weeks prior to admission, when he experienced the gradual onset of malaise and cough. After the development of marked dyspnea on exertion, blood-tinged sputum, and pain in the right upper quadrant of the abdomen, he was admitted to the Charity Hospital of Louisiana on March 21, 1963.

Physical examination revealed a thin, anxious, profusely sweating Negro man with a pulse of 170 per minute, a blood pressure of 110/85 mm. Hg, and a temperature of 100°F. The neck veins were markedly distended. Crepitant râles were heard at both lung bases. The heart was enlarged and a diastolic gallop rhythm was present, but there were no murmurs. The edge of the liver was firm, tender, and palpable 6 cm. below the right costal margin. The tip of the spleen was also palpable. The remainder of the physical examination was normal.

Laboratory studies revealed a hemoglobin of 13.7 Gm. per cent, a hematocrit of 44 per cent, and a white cell count of 5,350 per cubic millimeter, with a differential of 55 per cent neutrophils, 3 per cent band, 13 per cent eosinophils, 3 per cent monocytes, and 26 per cent lymphocytes. The urinalysis was normal. Multiple sputum smears and cultures were negative for acid-fast bacilli. Numerous other laboratory examinations were normal. An electrocardiogram showed first-degree A-V block, frequent multifocal premature ventricular beats, and a suggestion of left ventricular hypertrophy. A chest roentgenogram showed infiltrative changes throughout both mid-lung fields and cavitation in the right upper lobe; bilateral hilar adenopathy was noted. There was generalized cardiomegaly with a cardiothoracic ratio of 15.5/29 cm.

Hospital course. Initial therapy consisted of penicillin, digitalis, meralluride, meperidine, nasal

From the Departments of Medicine and Anatomy, Tulane University School of Medicine, the Charity Hospital of Louisiana, and the Seamen's Memorial Research Laboratory, United States Public Health Service Hospital, New Orleans, La.

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*Address: Department of Medicine, Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, La. 70112.

oxygen and bed rest The patient became afebrile and experienced some improvement on this regimen but continued to have a markedly prolonged P R interval and multifocal premature ventricular contractions (Fig 1 1) In view of the eosinophilia and the hilar adenopathy (Fig 1B) a lymph node biopsy was obtained which showed changes typical of sarcoidosis Clinical deterioration was rapid in spite of massive doses of steroids and a course of chloroquine Congestive failure and myocardial irritability persisted with varying degrees of A V block multifocal premature ventricular contractions and short runs of ventricular tachycardia The patient died on April 30 1963 shortly after developing acute pulmonary edema and complete heart block



Fig 1A Teleroentgenogram obtained on April 18 1963 showing cardiomegaly bilateral hilar lymphadenopathy pulmonary lesions pulmonary congestion and a cavity in the right upper lobe

Autopsy data Pertinent findings at postmortem examination performed 3 hours after death were confined to the lung the liver and the heart

Right (900 c c) and left (1 700 c c) serous pleural effusions were present Marked hilar adenopathy was noted The right lung weighed 650 grams and the left 965 grams There was bilateral pulmonary edema An area in the right upper lobe showed early cavitation Microscopically multiple focal noncaseating sarcoid granulomas were seen in both lungs and in the hilar lymph nodes Central fibrinoid necrosis was present in several of the granulomas Acid fast PAS and Gomori silver methenamine stain of multiple sections of lungs and hilar lymph nodes were all negative Cultures of the hilar lymph nodes were also negative for fungi and acid fast bacilli

The liver weighed 1 500 grams and showed evidence of passive congestion microscopic examination revealed small areas of periportal lymphocytic infiltration but definite granulomas were not identified

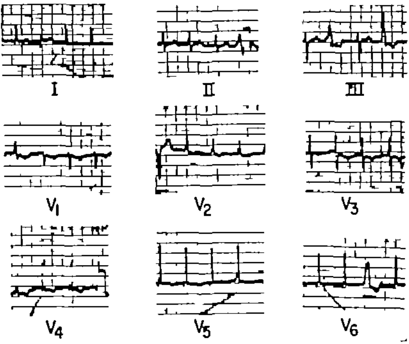


Fig 1B Electrocardiogram recorded on April 8 1963 Marked prolongation of the P R interval frequent multifocal ventricular premature contractions and T wave abnormalities are evident

The heart weighed 380 grams. There were many fibrinous adhesions between the epicardium and the pericardium. The coronary arteries were normal. The left and right ventricular wall measured 14 and 3 mm in thickness respectively. The circumference of the mitral valve was 12 cm, whereas that of the tricuspid valve was 13.5 cm; the aortic valve measured 7 cm and the pulmonary valve 7.5 cm in circumference. There were no valvular or endocardial lesions. Numerous confluent soft gray-white areas were present throughout the interventricular septum; smaller areas with similar characteristics were observed in the free walls of both ventricles; the anterior papillary muscle of the left ventricle was partially replaced by this whitish tissue. Microscopic examination of the heart revealed the presence of multiple areas (Fig. 2,*A* and *B*) of noncaseous granulomatous inflammation; giant cells of the Langhans type (Fig. 2,*A* and *B*) were observed in many of these granulomas. The process was particularly extensive throughout the interventricular septum (Fig. 2,*B*) but also involved the free wall of both ventricles, and there was a large grossly recognizable granuloma in the left atrial wall. The anterior papillary muscle of the left ventricle showed partial invasion by a granulomatous lesion. Areas of dense myocardial fibrosis (Fig. 2,*C* and *D*) which varied considerably in size and large numbers of chronic inflammatory cells were found in the interventricular septum and in the free wall of both ventricles. Some isolated myocardial fibers (Fig. 2,*C*) appeared trapped in these areas. Evidence of cellular damage in the form of loss of the striations and hyalinization of the fibers (Fig. 2,*C*) was observed in the heart muscle immediately surrounding the granulomas. The myocardium not involved in or adjacent to the infiltrative and fibrotic process appeared to be normal with very little evidence of fiber hypertrophy.

Histochemical and electron microscopic studies

Materials and methods. Samples of myocardium were obtained at autopsy from the interventricular septum and from the four chambers of the heart for histochemical study, electron microscopy and chemical determination of the serotonin, histamine and norepinephrine content.

HISTOCHEMISTRY. The following histochemical techniques were performed on fresh frozen cryostat sections of these tissues: (1) Unstained sections were examined by phase contrast and polarization microscopy for study of the general tissue structure. (2) Tissue autofluorescence of lipofuscin and elastic fibers was studied by fluorescence microscopy on unstained sections. (3) PAS reaction for carbohydrates. (4) Cresyl violet and toluidine blue stains for metachromatic substances. (5) Plasmal reaction for plasmalogens.[6] (6) Nile blue sulfate for lipids.[7] (7) Benzpyrene stain for the fluorescence microscopy of lipids.[8] (8) Cytochrome oxidase reaction.[9] (9) Succinic dehydrogenase reaction.[10]

ELECTRON MICROSCOPY. Tissue for electron microscopy was taken from the myocardium of the right and left ventricles and from the interventricular septum. Portions were selected from grossly normal and abnormal areas.

The tissues were fixed in 1 per cent phosphate buffered osmium tetroxide,[11] cut into 0.5 mm cubes, dehydrated in 70 per cent, 95 per cent and absolute ethanol and embedded in Maraglas.[1] Sections were cut with an L.K.B. Ultratome and examined with an RCA EMU 3C electron microscope.

Results

HISTOCHEMISTRY. The amount of lipofuscin observed was considered to be normal for the age of the patient. Study of the endocardium disclosed normal amounts of elastic tissue fibers. There was very little glycogen in the myocardium as estimated by the PAS reaction before and after amylase digestion. No accumulation of PAS positive substances was observed.

Cresyl violet and toluidine blue staining revealed the presence of numerous mast cells, often in groups of two or three, located at the border zones between the myocardium and the areas of granulomas and fibrosis. No mast cells were seen in the center of the granulomatous lesions and very few were found in the normal portions of the myocardium. The granules of the mast cells gave their usual strongly positive metachromatic reaction and appeared to be well preserved. No other metachromatic structures were observed in the myocardium.

The plasmal reaction was confined to the cardiac muscle fibers; the granulomas were negative except for the cytoplasm of the giant cells which was faintly positive. Many of the myocardial fibers at the border zones of the granulomas gave a very faint plasmal reaction (Fig. 3,*A*). The areas of fibrosis were consistently plasmal negative.

The fluorescent lipid stains, used because of their superior sensitivity, revealed the absence of fatty

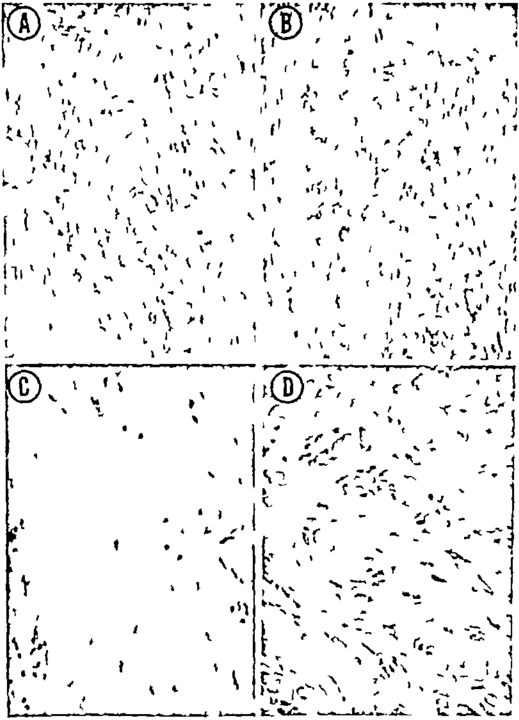


Fig. 2. *A*, Histologic section of the left ventricular wall demonstrating a typical well-circumscribed sarcoid granuloma. Hematoxylin and eosin ×100. *B*, Section through the interventricular septum showing the extensive involvement of the myocardium with the granulomatous process. Two giant cells and numerous inflammatory cells infiltrate the area. *C*, Section from the left ventricular wall showing heart muscle fibers surrounded by dense collagenous tissue and chronic inflammatory cells. The fibers have lost their striations and are small, atropic, and hyalinized. Hematoxylin and eosin ×200. *D*, View of left ventricular myocardium demonstrating the severe degree of interstitial fibrosis present throughout much of the heart. Hematoxylin and eosin ×100.

in the myocardium itself (Fig. 4, *A* and *B*). A unique finding essentially limited to areas of granulomatous invasion and fibrosis was the presence of numerous lipid droplets in the inflammatory cells and the cytoplasm of the endothelial cells of the myocardial capillaries (Fig. 4, *C* and *D*).

The abnormalities noted in the succinic dehydrogenase and cytochrome oxidase preparations were similar and consisted of a focal decrease in the intensity of the staining reaction of the myocardial fibers. This change was rather variable in degree and was essentially confined to the myocardium granuloma border zones. In these areas (Fig. 3, *B*) some cells had a relatively normal staining reaction, whereas others were completely devoid of enzyme activity and could be definitely identified as myocardial fibers only by polarization and phase-contrast microscopy, which revealed the presence of faint cross striations. Only giant cells in the inflammatory and granulomatous areas gave a positive reaction; the other cells produced only a trace of color with the two enzyme staining techniques. In the remainder of the myocardium the intensity of the reaction and the pattern of deposition of the reaction products were considered to be within normal limits by the methods used in this laboratory and by comparison with the results obtained in postmortem histochemical studies on the hearts of patients without cardiac disease.

ELECTRON MICROSCOPY. Sections taken from grossly normal areas of the myocardium contained muscle fibers showing various degrees of degeneration, as well as many which appeared to be essentially normal. The earliest electron microscopic evidence of myocardial degeneration consisted of swelling of the mitochondria (Fig. 5). The swollen mitochondria were evenly distributed within a given cell, although adjacent cells were sometimes affected to different degrees. In many cells

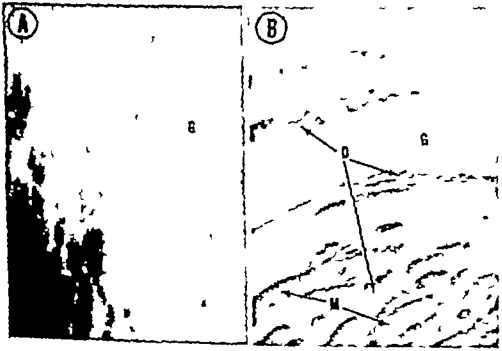


Fig. 3. Histochemical preparations from the left ventricle. *A*, Plasmal reaction (× [illegible]) showing the border zone between the myocardium and a sarcoid granuloma. The intense staining of the heart muscle fibers (*M*) fades out gradually as they merge into the area of granulomatous lesion (*G*) which is stained very lightly. *B*, Succinic dehydrogenase reaction (× [illegible]) demonstrating the normal staining reaction of the cardiac muscle fibers (*M*). At the bottom of the photomicrograph a few degenerating muscle fibers (*D*, arrows) are seen surrounded by granulomatous and fibrous connective tissue (*G*).

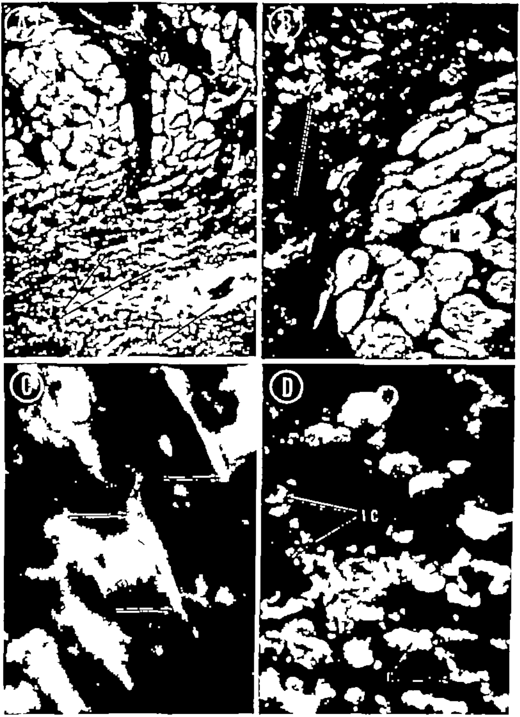


Fig 4 Fluorescence photomicrographs of sections of the left ventricle stained with benzpyrene for the fluorescence microscopy of lipids *A* An area of tissue similar to those in Fig 3 Normal myocardium (*M*) a small artery (*A*) and a small vein (*V*) are seen Numerous lipid droplets are visible in the inflammatory cells and in the walls of the capillaries (*C*) ×200 *B* Normal staining reaction in the myocardial fibers (*M*) lipid in the muscle (*M*) is localized to the interfibrillary spaces and the mitochondria No neutral lipid droplets are present in these fibers Lipid droplets are seen in the adjacent zone of inflammation (*arrows*) ×450 *C* An early stage of deposition of lipid droplets in the walls of capillaries (*arrows*) ×1 000 *D* An advanced stage of the accumulation of lipid droplets in the walls of capillaries (*C*) and in some inflammatory cells (*IC*) ×1 000

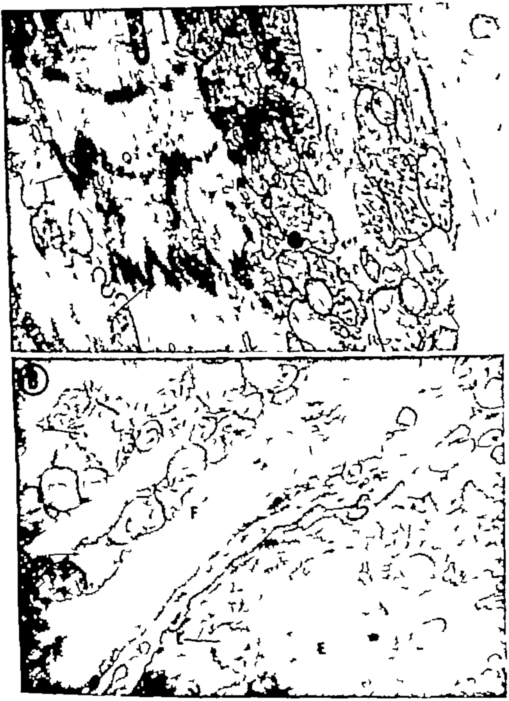


Fig 5 *A* Electron micrograph showing the increased osmophilia of the areas adjacent to the intercalated discs (*arrow*) ×16 000 *B* Electron micrograph longitudinal section of myocardium showing a capillary with an erythrocyte (*E*) in its lumen adjacent to a degenerating muscle fiber (*F*) Note the almost complete absence of striations and the swollen mitochondria (*arrows*) among the normal appearing ones A large lipid droplet (*L*) can be seen in the cytoplasm of a capillary endothelial cell ×17 000

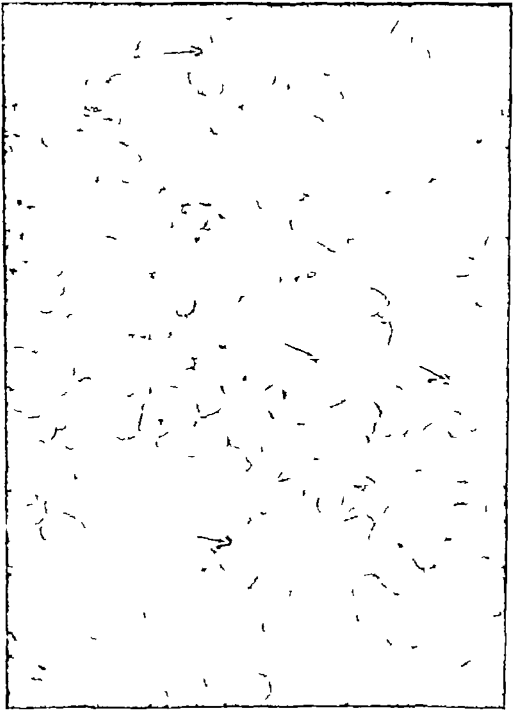


Fig. 6. Longitudinal section of a muscle fiber. Electron micrograph showing areas of increased osmiophilia (arrows). These areas are often, but not always, associated with the Z band. ×20,000.

small foci of increased electron density were present in some of the myofibrils (Figs. 6 and 7). At these points the myofilaments were obscured and sometimes appeared to be disrupted. These foci were often very small, extending longitudinally less than one half of the length of a sarcomere and involving only a small fraction of the cross-sectional area of the myofibril. Usually, cells thus affected also contained

similar foci of increased density immediately adjacent to the intercalated discs (Fig 5 B) so that the discs stood out in sharp contrast to the rest of the fiber

The myocardial cells found in sections taken from the periphery of the granulomatous lesions were more severely diseased and contained many vacuoles mitochon



Fig 7 Electron micrograph of part of two adjacent muscle cell separated by an extravasated erythrocyte (*E*) One fiber (*lower right*) appears to be relatively normal whereas the other (*upper left*) is severely damaged Note the marked vacuolization (*V*) the areas of increased osmophilia (*O*) and the absence of striations in the damaged fiber ×18 000

drial fragments and swollen mitochondria (Fig 7) The total number of mitochondria was markedly reduced in these cells The myofibrils no longer contained the dense areas described above except at the intercalated discs but all striations were indistinct and the myofilaments often appeared to have dissolved into a homo

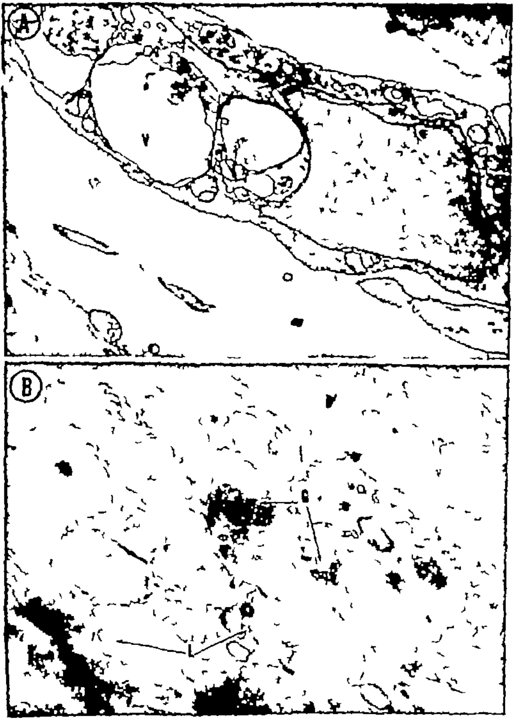


Fig 8 *A* Electron micrograph of an infiltrating cell from the edge of a granulomatous nodule Note the vesiculation (V) and lack of organization of the cytoplasm ×10 000 *B* Part of a mast cell from the edge of a granuloma The granules appear typical containing both the granular (*G*) and the lamellar (*L*) components ×42 500

geneous mass The over all size of such muscle fibers was greatly decreased

The intercellular space in the areas of inflammation was increased in amount and contained many interstitial cells of many sizes and shapes usually surrounded by dense bundles of collagenous fibers In some areas the collagenous fibers were

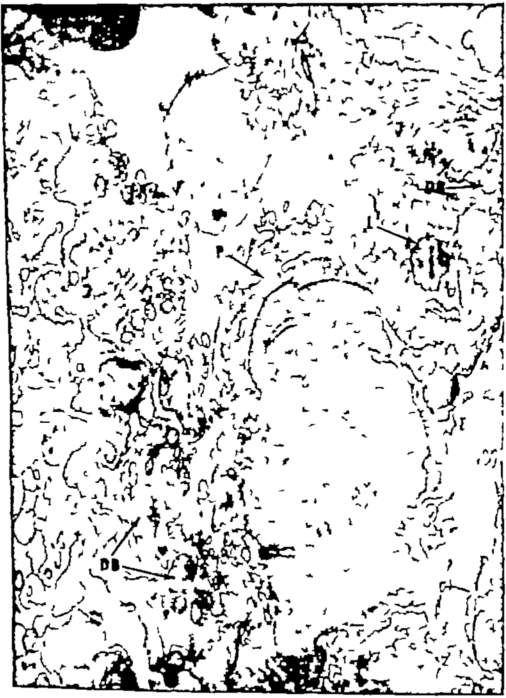


Fig 9 Cross-section of a capillary from an area similar to those shown in Fig 4 Note the large lipid droplet (L) and the dense spherical bodies (DB) which probably represent lysosomes Numerous pinocytotic vesicles (P) are present near the luminal surface of the capillary endothelium ×16 000

so numerous that they made up the bulk of the tissue.

The interstitial cells (Fig. 8 *A*) were found sometimes singly, sometimes in small clusters. The nuclei were irregular in shape; the chromatin was finely granular and evenly distributed. Nucleoli were seldom observed. The cytoplasmic elements showed little ultrastructural organization. The morphology of mitochondria was variable, but in general very few cristae were evident, usually not over four or five in each mitochondrion. The endoplasmic reticulum was present in the form of small vesicles, some of which were studded with ribosomes. No distinct Golgi apparatus was seen, although it might have been represented by some of the smooth-walled cytoplasmic vesicles. Cytoplasmic vacuoles (Fig. 8 *A*), some of which were almost as large as the nucleus, were present in large numbers. Myelin figures and lipid droplets were not uncommon. Mast cell granules had a normal appearance (Fig. 8 *B*).

Capillaries were frequently encountered in the interstitial spaces (Figs. 5 *B* and 9). The endothelial cells of these capillaries differed from those of normal myocardium in two respects. Pinocytotic vesicles were present throughout the cytoplasm in much greater numbers than in the capillaries of normal areas. Lipid droplets were also present in the cytoplasm of the endothelial cells (Figs. 5 *B* and 9), sometimes in great numbers. It was not uncommon to encounter lipid droplets of comparable size in the lumen of these capillaries.

BIOCHEMICAL ANALYSIS. Results of chemical analyses performed by Dr. Albert Sjoerdsma* at the National Institutes of Health, Bethesda, Maryland, showed that a tissue sample pooled from the four chambers of the heart contained 0.25 μg of norepinephrine, 1.90 μg of histamine, and less than 0.05 μg of serotonin per gram of myocardium.

Discussion

It is impossible to determine in what manner the therapy administered to the patient may have contributed to, or otherwise altered, the extensive myocardial degenerative changes observed in the contractile elements, the mitochondria, and the capillary endothelium.

The ultrastructural alterations in the myofibrils are of particular interest since, to our knowledge, these changes have not been reported previously. Spotty degeneration of the myofilaments might represent the earliest electron microscopic evidence of hyalinization of the myocardial fibers, but no intermediate stages were observed between this and the extensive dissolution of the myofilaments seen in more severely damaged areas. It is entirely possible that the two phenomena occurred independently. There is no satisfactory explanation for the greater frequency of such alterations in the regions immediately adjacent to the intercalated discs.

The mitochondrial changes described represent the manifestations of myocardial cell injury and death. The association between mitochondrial swelling and myocardial injury has been discussed in detail elsewhere.[12] Mitochondrial swelling is most likely a nonspecific phenomenon that may be to some extent reversible by natural and completely unknown processes of repair. More advanced mitochondrial alterations, such as pronounced swelling, loss of the cristae, and fragmentation, are probably indicative of irreversible cellular damage. The histochemical manifestations of the mitochondrial abnormalities consisted of a decrease in the intensity of the staining reaction for plasmalogens and for the two mitochondrial enzymes tested, i.e., succinic dehydrogenase and cytochrome oxidase. This decrease in enzyme activity probably constituted histochemical evidence of mitochondrial damage. This is considered to be an intermediate stage between normal staining and the disappearance of these enzymes, as described in detail in human myocardial infarction[14,15] and in experimental myocardial necrosis.[13,16] On the basis of electron microscopic studies on the morphology of cardiac tissue in postmortem specimens[16] and of histochemical observations concerning the preservation of succinic dehydrogenase activity in heart muscle at various times after death,[14] it is reasonable to conclude that these mitochondrial changes are not the result of postmortem autolysis.

*We are grateful to Dr. Sjoerdsma for [illegible] help [illegible] performing these analyses.

Abnormalities of the myocardial capillaries demonstrate another peculiar type of alteration for which there is no definite explanation. It is known that the type of lipid deposition found in the capillaries of the myocardium does not occur in normal[17, 18] growing or regenerating capillaries.[18] Of great interest, however, is the fact that very similar electron microscopic alterations in the capillary endothelium, including the lipid deposition, have been produced experimentally by the local application of serotonin or histamine.[4]

The amine analyses were undertaken since mast cells rich in histamine and serotonin[1, 20] were found in the myocardium surrounding the granulomatous areas. Increased numbers of these cells are known to be present in a variety of chronic inflammatory states including tuberculous and syphilitic granulomas,[20, 3] but their functional role has not been clarified.

Interpretation of the data obtained for serotonin and histamine is rendered very difficult by the paucity of information on the content of these amines in normal myocardium. The serotonin content of dog *myocardium* has been estimated[4] to range from 0.06 to 0.35 μg per gram of tissue. The concentration of histamine in the heart of several animal species varies[4] from 1 to 10 μg per gram of myocardium. There is a wide variation within a given species. There appear to be no studies of this nature for *human hearts*. Of more importance than tissue levels is the fact that mast cells accumulated in the vicinity of injured myocardial cells. This raises the possibility that the biologically active amines present in the mast cells could have attained high concentrations in these areas. Thus they might have contributed to the pathogenesis of the endothelial and myocardial cell injury and to the clinical manifestations of cardiac irritability. The patient received large doses of steroids which are known to cause degranulation of mast cells as well as a significant reduction in myocardial mast cell counts. It is possible, therefore, that mast cells would have been present in even greater numbers had steroids not been used.

The low concentration of myocardial norepinephrine is of particular interest in view of the observations of Chidsey and associates[8] on the norepinephrine content of normal and failing human hearts. Mean norepinephrine concentrations of 1.82 ± 0.8 μg per gram of myocardium were reported for normal hearts and of 0.53 ± 0.47 μg per gram of myocardium for failing hearts. It has been postulated[8] that the decrease in myocardial norepinephrine may be due to the hyperactivity of the sympathetic nervous system which occurs in congestive heart failure and that the depletion of these amines may contribute to further impairment of myocardial function. Although the level of norepinephrine obtained in our case certainly falls within the range found by these investigators in failing hearts, the role of drug therapy in the genesis of these changes must be considered.

Because of the limited nature of the data obtained in this study, the preceding considerations on the nature of the alterations observed in the myocardium must remain within the realm of conjecture. It is obvious that much work remains to be done on the histochemical and electron microscopic features of sarcoid heart disease before some of the problems discussed above can be answered.

Summary

For the first time histochemical and electron microscopic investigations on the heart muscle of a young patient with sarcoidosis and congestive heart failure were made and correlated. The studies disclosed extensive myocardial damage, a large portion of which was irreversible. Swelling of muscle mitochondria was noted, followed by disruption of the mitochondrial structure and loss of the mitochondrial enzymes. Various alterations were evident in the contractile elements. Lipid droplets and increased numbers of pinocytotic vesicles were observed in some of the capillaries of the heart. Numerous mast cells were found in the myocardium bordering the sarcoid granulomas. The significance of these findings was discussed.

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Complications in 4,413 catheterizations of the right side of the heart

Alf Wennevold, M.D.
Ib Christiansen, M.D.
Ole Lindeneg, M.D.
Copenhagen, Denmark

During the past 20 years, catheterization of the right side of the heart has obtained a foothold as a routine procedure in cardiac disease, and the commonly held opinion is that catheterization of the heart involves but few and mostly minor complications. A numerical evaluation of the risk has been made previously on the basis of limited materials or by aggregate surveys from several laboratories. In our laboratory, 4,413 catheterizations of the right side of the heart have been performed during 16 years, and the purpose of the present study was to investigate the frequency of complications in a comprehensive and homogeneous material.

Material

Over the period from Feb. 13, 1947, until March 31, 1963, 4,413 catheterizations of the right side of the heart were performed in 3,197 patients, mostly adults and older children. Less than 5 per cent of the patients were under 5 years of age; the youngest was 3 months and the oldest was 80 years.

There were 1,602 female patients and 1,595 male patients.

Patients with all types of heart disease were examined; most frequently, catheterization of the right side of the heart was applied for the diagnosis of congenital heart disease (Table I).

The present report comprises all examinations in which the heart was examined via a peripheral vein. Five hundred and seventy-seven of the catheterizations were concluded with angiocardiography in collaboration with the Department of Diagnostic Radiology. An analysis of the complications of selective angiocardiography was previously published by Davidsen and associates.[4]

Method

The catheterization was performed via a peripheral vein in a limb. Local anesthesia was applied and, as premedication, small doses of phenobarbital were given. Cournand and Lehman catheters were used under direct visualization by fluoroscopy. During the entire examination the electrocardiogram (primarily Standard Lead II) was monitored on an oscilloscope. The catheter was flushed with heparinized saline solution at intervals of a few minutes.

Complications

I. Deaths. Five deaths occurred which were related in time to the examination. Two of these occurred in direct connection

From the Cardiological Laboratory, Department of Medicine B, University Hospital, Copenhagen, Denmark.
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with the examination, whereas the causal relationship was uncertain in 3 cases. Death occurred in 3 cases among the 517 examinations which were concluded with angiocardiography. These latter 3 cases have been reported previously (cf. Table II).

Table I. Diagnosis in 3,197 catheterized patients

Diagnosis	Number of heart catheterizations		Number of patients	
Congenital heart disease	2,473		1,677	
Acquired heart disease	1,706		827	
Rheumatic		969		648
Arteriosclerotic and hypertensive		34		32
Other causes		703		147
No heart disease	734		693	
Totals	4,413		3,197	

Table II. Fatal complications in right heart catheterization with and without angiocardiography

Case number	Sex	Age (yr.)	Diagnosis	Angiocardiography
3356	F	14	Patent ductus arteriosus, pulmonary hypertension	
4399	M	8	Fallot's tetralogy	
376	M	31	Cor biloculare, patent ductus arteriosus	
3744	M	46	Rheumatic aortic stenosis and insufficiency	
3819	M	55	Cancer of the lung	
3383	M	2	Tricuspid atresia	+
4587	M	17	Isolated pulmonary stenosis	+
5984	F	7	Patent ductus arteriosus, atrial septal defect, pulmonary hypertension	+

*Published by Davidsen and associates and Tybjaerg Hansen and Warburg.[illegible]

Case No. 3356. A patent ductus arteriosus had been ligated 6 years previously. After the operation catheterization of the heart revealed pulmonary hypertension (80 mm. Hg). Prior to admission there had been daily episodes of syncope, dyspnea, and cyanosis. During the examination the right atrium was catheterized via a left superior caval vein and sinus coronarius. The pressure was 19 mm. Hg, and further exploration was discontinued. There were no complaints in connection with the examination, but 4 hours later the patient went into a syncopal attack and cardiac arrest occurred shortly afterward.

Case No. 4399. One year after a successful radical operation for Fallot's tetralogy, catheterization of the right side of the heart was performed in order to evaluate the result of the operation. The catheter was introduced from the left arm via a left superior caval vein and sinus coronarius through the tricuspid orifice. Thereat runs of ventricular extrasystoles were provoked, eventuating in ventricular tachycardia. The tachycardia did not respond to procaine amide, cardiac decompensation developed, and the condition was not improved in spite of digitalis and quinidine. Six days later bradycardia set in, and cardiac standstill occurred shortly afterward. The case has been published by Poulsen and associates.[illegible]

Case No. 376. The patient had congenital cyanotic heart disease with several defects. Increasing cyanosis and congestive heart failure were observed. The examination revealed pulmonary hypertension and failure of the right ventricle. During catheterization chill and a brief rise in temperature set in. Two days later the patient died in cardiac decompensation.

Case No. 3744. The patient was catheterized while in severe cardiac decompensation which increased after the examination. He died suddenly 7 days later.

Case No. 3819. The patient was in a serious general condition and was catheterized in order to evaluate the function of the healthy lung. While the catheter was situated in the right ventricle, ventricular fibrillation set in suddenly. Open-chest massage of the heart was given, during which sinus rhythm occurred. On the sixth day the patient had apparently recovered completely—but during the subsequent day his condition deteriorated gradually, and death occurred 10 days after the catheterization.

Autopsy was performed in 4 of the cases. No lesions of vessels or heart due to the catheterizations were found.

II. Cardiac irregularities and conduction disturbances. During all the catheterizations the patients' electrocardiograms were continuously monitored on an oscilloscope, and disturbances in the rhythm of any appreciable duration were recorded. The arrhythmias were uniformly distributed over the various heart diseases (Table III).

Attacks of *supraventricular tachycardia* occurred during 62 catheterizations in 57

patients One patient with an atrial septal defect had supraventricular tachycardia in connection with all of the 4 catheterizations which he underwent and in another 2 patients tachycardia occurred during both their examinations During subsequent examinations 3 patients had other types of arrhythmias

Twenty out of the 59 patients had had spontaneous attacks of arrhythmia The patient who had tachycardia during 4 heart catheterizations had not had tachycardia previously

Attacks of *atrial fibrillation* occurred in 20 cases During previous catheterizations 2 of the patients had had runs of extrasystoles which prevented catheterization of the pulmonary artery

Nine of the patients had had spontaneous attacks of rapid or irregular heart action

Atrial flutter occurred during 13 examinations of 12 patients One patient—a 22 year old man with normal findings at catheterization—had experienced rapid heart action on previous occasions

In all cases the supraventricular arrhythmia ceased in less than 48 hours In some cases the attacks were treated with digitalis or quinidine (Table III)

Conduction disturbances in the form of complete atrioventricular block and right bundle branch block occurred during 21 catheterizations all cases being of short duration

Ventricular fibrillation occurred in 2 patients Case No 3819 was discussed above

Case No 5661 One year after mitral valvulotomy this 42 year-old woman was catheterized because of recurrent progression of symptoms During catheterization of the ventricular orifice ventricular fibrillation set in With the use of artificial respiration and external cardiac massage the blood pressure was 50 mm Hg and after 5 minutes the pupils dilated During subsequent direct cardiac massage the wall of the right ventricle was torn in two places where there were pericardial adhesions After suture of the tears A C defibrillation was performed and trial fibrillation set in as before the examination During the subsequent course no signs of cerebral damage were observed and the heart function was unchanged

Ventricular tachycardia occurred in 2 cases one with a fatal outcome (Case No 4399) In the other case the tachycardia lasted for a few minutes

Extrasystoles have been included in the table only when they were of longer duration or interfered with the examination

III Other complications (*cf* *Table IV*) One hundred thirteen instances of *febrile*

Table III Arrhythmias and conduction disturbances as complications in 135 right heart catheterizations

Arrhythmia	Catheterizations (number)	Position of the catheter: Right atrium (number)	Right ventricle (number)	Pulmonary artery (number)	Other place (number)	Duration: Minutes (number)	Hours (number)	Days (number)	Treatment: None (number)	Medicine (number)	Thoracotomy (number)	Catheterizations discontinued (number)
Supraventricular tachycardia	6?	34	16	3	9	44	13	5	44	18	–	1
Atrial fibrillation	20	9	2	6	3	4	5	11	6	14		7
Atrial flutter	13	5	3	1	4	10	2	1	12	1		3
Atrioventricular block		2	3	–	2	7	—	—	7	—		2
Right bundle branch block	14	5	4	1	4	9	5	—	14	—		3
Ventricular fibrillation	2	—	2	–	–	2	—	—	—	—	2	2
Ventricular tachycardia	?	1	1	–	–	1	—	1	1	1	–	1
Extrasystoles	15	2	6	1	6	14	1	—	15	—	–	4

Table IV. Complications apart from arrhythmias

Complication		
Rise in temperature to 38 C. or more—with or without chills	113	
Spasm of the vein	89	
Vasovagal attacks	24	
Chills	16	
Wound infection	12	
Thromboembolic complications	9	
Skin affection	7	
Occlusion of the pulmonary artery by catheter	5	(6)
Lesion of artery	3	
Precordial pains	4	
Excessive bleeding	3	
Pulmonary edema	3	
Perforation of the myocardium	2	
Lesion of nerve	1	
X-ray accident	1	

reactions with or without chills, usually subsiding 24 hours after catheterization, and 16 instances of isolated chills in connection with catheterization were recorded.

By far the majority of febrile reactions occurred during the first years; thus, 86 cases of elevated temperature occurred over the years 1947 to 1954. Since 1960 only one or two cases have occurred annually.

Venous spasm occurred most frequently when the veins were small or of an irregular course, or in cases in which the surface of the catheter was uneven, in connection with prolonged examinations, or when the examiner was inexperienced. As a rule, the spasm subsided after intravenous injection of meperidine. In a few cases further local infiltration of procaine at the site of incision has been applied.

As for *vasovagal attacks*, bradycardia, a fall in blood pressure, pallor, and in some cases, nausea or vomiting occurred in connection with 24 catheterizations. Most of these complications (17) occurred because of irritation of an artery. In 5 cases these complications occurred without direct provocation at the end of a particularly protracted examination, and 2 attacks occurred during isolation of deep veins. The episodes lasted for a few minutes; in 11 cases they disappeared spontaneously, and in the other 13 cases they subsided rapidly after the intravenous injection of atropine.

Three cases of loss of consciousness, convulsions, and asystole lasting between 20 and 60 seconds were seen. Twelve of the patients had had previous episodes of unconsciousness.

Superficial venous thromboses extending less than 3 or 4 cm. are not included among the *thromboembolic complications*. More extensive thromboses were seen in 6 cases, but no propagation to profound veins was observed. Furthermore, a 46-year-old man with atrial septal defect, a 41-year-old man with rheumatic aortic insufficiency, and a 35-year-old woman with mitral stenosis exhibited moderate symptoms of lung infarction during the first days.

Skin affection was observed in 7 patients, 4 of whom developed exanthema due to iodine at the site of incision.

At the end of the examination, 1 patient had an urticarial exanthema on the abdomen, which disappeared spontaneously. This patient often had urticaria without any demonstrable cause, as well as a slight bronchial asthma.

During the determination of shunting by the dye-dilution method, 1 patient with atrial septal defect received a second degree burn on the ear from the earpiece of the oximeter, which had been applied for 30 minutes. The wound healed without any complications.

One patient developed a necrosis of the skin around the site of exposure of the vein after injection of 3 ml. of 20 per cent potassium oxalate, the ampules of which had been mistaken for those of local anesthetic.

Occlusion of the pulmonary artery by the catheter occurred in 5 patients who collapsed after the catheter had been introduced into the pulmonary artery through a pulmonary stenosis. All of them recovered promptly upon withdrawal of the catheter. However, in 1 patient asystole developed, but the heart action reappeared after blows were given over the precordium (this case is published by Fabricius, Hansen, and Warburg[19]). Four of the patients had Fallot's tetralogy, and 1 had a ventricular septal defect and pulmonary stenosis.

The 5 patients had a gradient across the pulmonary orifice greater than 75 mm. Hg, and their electrocardiograms showed QRS axes of more than 120 degrees. Fur-

thermore there was right ventricular strain In 3 of these patients subsequent operation or autopsy verified that there was a particularly narrow pulmonary stenosis which might have been occluded by a catheter

In a sixth patient (Case No 6503) a 12 year old boy with a large ventricular septal defect and pulmonary stenosis a similar episode occurred Later on a slight valvular stenosis was found at autopsy The pressure gradient across the stenosis was determined to be 40 mm Hg the QRS axis in his electrocardiogram was 90 degrees and he had a slight ventricular strain We can offer no explanation of this episode

In the matter of *lesions of the arteries or nerves* an artery was mistaken for a vein and injured in 3 instances The vessel was sutured and there were no sequelae In 1 case a nerve was injured and the patient developed impaired sensibility on a limited area of the forearm

Precordial pains occurred in 3 patients (Slight oppression or indisposition is not included)

Cases Nos 6672 and 5811 Two patients a 17 year old boy and a 29 year old woman both suffering from atrial septal defect experienced precordial pains as the catheter was passed through the defect to the left atrium The pains disappeared when the catheter was withdrawn to the right atrium and after meperidine had been administered During the attack of pains the woman had also an elevation of the S-T segment which lasted for 10 minutes

Case No 4319 This 56 year-old woman with a slight constrictive pericarditis experienced precordial pains which radiated to the left arm and the back as occurred with bundle branch block when attempts were made to pass the tip of the catheter from the conus of the right ventricle into the pulmonary artery The catheter was withdrawn and glyceryl nitrate was administered with immediate effect The bundle branch block disappeared after withdrawal of the catheter Previously the patient had often had precordial pains and had taken glyceryl nitrate for many years

Loss of blood requiring treatment was a complication in 3 cases The loss of blood was so large in connection with catheterization in children that blood transfusion had to be given

Pulmonary edema developed in 3 patients all of whom were suffering from a left valvular disorder with a moderate to severe increase in pressure in the pulmonary circulation The examination was discontinued and the pulmonary edema disappeared after an injection of morphine

Perforation of the myocardium by the catheter happened in 2 cases

Case No 6649 This 53 year-old woman with mitral stenosis belonged in functional Group III While a Cournand catheter was being bent in the right atrium the catheter perforated the atrial wall and entered the pericardial cavity The patient felt a brief and slight pricking and when the catheter was passed toward the parietal pericardium she experienced oppressive pains in the precordium Twenty milliliters of slightly sanguinolent serous fluid was aspirated and during withdrawal a mean pressure of 0 mm Hg was measured in the pericardial cavity and 7 mm Hg in the right atrium The catheter was removed and on inspection no defects of the material were found The patient was unaffected During the next 2 days she ran a

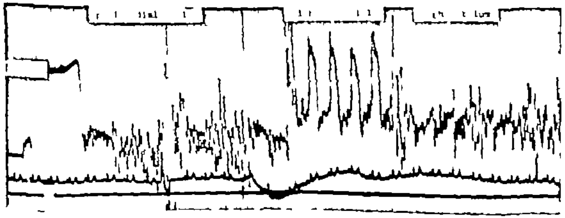


Fig 1 Case No 6745 Pressure recording during withdrawal of catheter from the pericardial cavity to the right ventricle and right atrium

slight temperature, the electrocardiogram, auscultatory findings, and an x-ray film of the chest were as prior to the catheterization. Eleven days later the patient developed recurrent emboli in the pulmonary arteries. Three months later she died in cardiac incompetence. Autopsy revealed lung infarctions, severe mitral stenosis, and slight tricuspid stenosis. The right atrium was enlarged and the wall was hypertrophic; there were no signs of lesions of the wall or of parietal thromboses. The pericardial cavity contained 100 ml. of slightly sanguinolent serous fluid.

Case No. 6745. This 37-year-old man complained of episodes of irregular heart action accompanied by a pricking sensation in the precordium and dyspnea. During catheterization of the right atrium with a Cournand catheter, supraventricular tachycardia *set in and lasted for 30 seconds.* When the catheter was withdrawn across the pulmonary valve, a run of ventricular extrasystoles occurred; the catheter was at once advanced and sinus rhythm was re-established. Surprisingly, a pressure of a few millimeters of mercury was then measured and the patient had pricking pains in the chest; nothing could be aspirated through the catheter. During withdrawal of the catheter the pressure was recorded (Fig. 1) and the examination was concluded. The patient experienced a slight oppression in the precordium. X-ray examination of the chest the next day revealed slight density of the left phrenicocostal sinus; this subsided after another week. Physical examination and electrocardiography showed normal conditions when the patient was seen for the last time 6 months after catheterization. Because the catheter that had been used was very stiff on its outermost 10 cm., it was discarded.

Overdosage of roentgen took place in 1 case.

Case No. 1477. This 25-year-old man who had no cardiac disease was exposed to continuous fluoroscopy for 1 hour on account of faulty adjustment of the apparatus and received a total of 180 r. He remained completely well without signs of burns. During the following 4 weeks a slight transient fall in leukocytes was observed. At examinations in various hospitals over the next 9 years the blood count was normal.

Discussion

Fatal complications. In the present material[1] comprising 4,413 catheterizations of the right side of the heart, 2 deaths occurred which were directly related to the examination (0.045 per cent). Furthermore, 3 deaths occurred within the next few days after the catheterization. Two of the latter patients belonged to the group with severe cardiac incompetence and it cannot be decided whether the catheterization was a contributory cause of death.

From 12 Swedish hospitals Bagger and associates[1] collected a material from 1947 to 1956 consisting of 5,859 cases of catheterizations of the right side of the heart among which there were 5 deaths (0.09 per cent) attributable to the examination. The investigations of Cournand and associates[6] show a mortality of the same order of magnitude. The right heart catheterizations of Seebat and associates[18] seem to be encumbered with a higher mortality, but it does not appear with certainty from their material how many deaths can be ascribed to the examination.

The purpose of the present study was not to estimate the risk of angiocardiography, and complications that occurred during such examinations are mentioned only in cases with fatal outcome. As stated above, the examination was supplemented by angiocardiography in 577 cases in this laboratory, and 3 complications with a fatal outcome occurred (0.52 per cent), a mortality rate of the same order of magnitude as that seen in the material of Bagger and associates.

A number of authors[5,8,17] have reported a high mortality in connection with heart catheterization in patients with Ebstein's disease. In our material no deaths occurred in connection with 24 catheterizations in such patients, so that we are unable, therefore, to confirm a considerable risk in such cases.

Neither can we on the basis of 28 catheterizations in patients with primary pulmonary hypertension confirm the great risk reported by others.[3,4,7,19]

Deaths have occurred among patients with incompetence of the right side of the heart in a couple of cases during the 24 hours preceding a planned heart catheterization without it being possible to demonstrate other relations to the examination than the time relation. Therefore, it is probable that death which occurs in patients with severe cardiac incompetence must be ascribed to the patient's condition rather than to the examination itself. On the whole, the risk of fatal complications is slight.

Arrhythmias and conduction disturbances. Arrhythmias of all types may occur during catheterization of the right heart and, as a rule, extrasystoles are observed.[8,11,12,14,20]

Of the arrhythmias only ventricular fibrillation and ventricular tachycardia are connected with risk of death or late sequelae. It must be emphasized, however, that the electrocardiogram should be watched continuously during the entire examination so that measures can be taken at once in case of arrhythmia. In the few cases in which catheterization of the right ventricle cannot be performed without the occurrence of runs of extrasystoles, further catheterization must be abandoned. Although the dangerous forms of arrhythmia are rare, they are amenable to efficient treatment, and in any laboratory in which heart catheterizations are performed there should be access to treatment by means of electrical stimulation of the heart and to assistance from chest surgeons.

In our material 20 of the 59 patients who developed supraventricular tachycardia and 9 of the 20 patients with atrial fibrillation had previously had spontaneous arrhythmias. This indicates that there is an increased risk of the occurrence of arrhythmias in such patients during catheterization.

Other complications. Our material comprises only few pyrogenic reactions. In this material, as in the series of other authors, the frequency is highest during the first years. An abrupt fall in the number of reactions was seen when we began to make sure that the catheters were thoroughly cleaned *immediately* after they were removed from the vein. According to the experience of Seebat and associates,[4] pyrogenic reactions may be a serious complication in severe cardiac incompetence.

Perforation of the myocardium to the pericardial cavity is a rare complication in our material as well as in the material of other authors. Because heart tamponade may ensue, careful observation, including evaluation of the size of the heart by means of x-ray examination, is necessary, so that surgical treatment can be performed in due time.

Summary

The frequency of complications in a material consisting of 4,413 catheterizations of the right side of the heart performed in the same laboratory over 16 years is reported.

The patient material consisted mainly of adults and older children. Two thirds of the patients had a congenital heart disease and one third had an acquired heart disease.

Two deaths occurred in direct connection with the examination (0.045 per cent). During the days which followed the examination 3 severely ill patients died, but there was no reason to assume that these deaths were caused by the examination.

Apart from single extrasystoles, arrhythmias occurred in 135 cases (3 per cent). The arrhythmia was considered to be perilous in 4 cases (0.09 per cent): 2 cases of severe arrhythmia were ventricular tachycardia, one of which had a fatal outcome. The other 2 cases were ventricular fibrillation; both patients survived after cardiac massage and A.C. defibrillation, but one of them died 10 days later.

Lesions of the heart produced by the catheter occurred twice; in both cases the heart wall was perforated and the course was benign.

The risk of death or late sequelae in connection with heart catheterization is slight. Dangerous complications may arise, however, and heart catheterization should therefore be performed only when there is access to treatment with electrical stimulation of the heart and to assistance from chest surgeons.

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Electrocardiographic changes during daily work and acute exercise in permanent inhabitants of hot areas

*Mordechai Toor, M.D.**
Joseph H. Yahini, M.D.
Ilhar Zahavi, M.D.
Shaul Massry, M.D.
Jacob Agmon, M.D.
Petah Tiqva, Israel

The effects of work,[1] heat stroke,[2] and dehydration[3] on the electrocardiogram have been described, but there have been only a few studies concerned with the chronic effects of a hot environment on the electrocardiograms of permanent inhabitants of hot areas.

The aim of this study was to investigate the electrocardiographic changes seen in young and healthy permanent inhabitants of hot areas during their daily work and after acute effort under different conditions of hydration.

Material and methods

Field studies were conducted in Sodom, which is situated 400 meters below sea level in the Dead Sea area, and in Timna, which is near Eilat in the Red Sea area, during the hottest summer months of 195? 1960.

The meteorologic data on the regions concerned during the experiments are given in Table I.

In order to evaluate the effect of chronic exposure to environmental heat, 56 male subjects (age range of 21 to 34 years, mean 27) were studied before and after work in Sodom and Timna during 189 working days. They worked on different shifts: morning shift from 7 A.M. to 3 P.M., afternoon shift from 3 P.M. to 11 P.M., and night shift from 11 P.M. to 7 A.M. The effect of acute heat stress was investigated in 4? male subjects (age range of 22 to 33 years, mean 26) in 71 walking experiments consisting of a 2 hour hike at a speed of 6 kilometers per hour between 11 A.M. and 1 P.M.

All participants were permanent residents of the hot areas and had been engaged for many years in the same type of physical labor in the potash works at Sodom and the copper mines in Timna. Before the experiments they underwent a thorough physical examination and were found to be healthy.

Hydration conditions. The working experiments were carried out under the following drinking conditions: (a) restricted water intake (Restricted W. I.), (b) free water intake (Free W. I.), (c) forced water intake (Forced W. I.)—drinking more than thirst urge without provoking n[illegible]

From the C[illegible] Laboratory and The [illegible] of [illegible] and Health and E[illegible], Petah Tiqva, Israel.
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*Address: C[illegible] Laboratory, [illegible] Hospital, P. O. B. [illegible], Petah Tiqva, Israel.

Table I Meteorologic data Working and walking experiments

Locale	Shift	Dry bulb temp (C)	Wet bulb temp (C)	Relative humidity (%)	Wind speed (Km/hr)
Working Experiments					
Sodom	Morning	34 6–37 1	20 0–33 0	15–51	0–33 6
Sodom	Night	30 8–31 2	20 0–25 2	21–53	0–24 0
Timna	Morning	30 5–32 7	17 2–26 4	12–56	0–33 6
Timna	Afternoon	32 4–35 7	19 2–23 0	13–45	24–33 6
Walking Experiments					
Timna	11 A M–1 P M	36–38	18 8 22 2	15–34	24
Timna	11 A M–1 P M	38–40	21 8–22 4	20–33	24 0–33 6
Sodom	11 A M–1 P M	40–43	21 5–23 0	20–29	3 2–24 0
Timna	11 A M–1 P M	45–47	22 0–26 7	14–34	8 6–16 0

The drinking conditions set up for the walking experiments were as follows (a) no water intake (No W I) (b) free water intake (Free W I) (c) forced water intake (Forced W I)

In order to exclude variations in response to heat stress under different conditions of hydration related to individual factors the same subjects were asked to repeat the same work and walk at the same temperature but under different conditions of hydration A total of 82 working and 20 walking repeated experiments were performed by 58 subjects

A standard 12 lead ECG was recorded in all subjects before and within 15 to 30 minutes after the experiments on a Sanborn direct writing apparatus The following features were analyzed before and after the experiments heart rate P R interval corrected Q T interval QT/TQ ratio S T and T changes frontal axis of P QRS and T as well as direction and magnitude of the ventricular gradient The measurements were made in 5 consecutive complexes of the chest leads and the average value was taken The corrected Q T interval was determined according to Bazett s formula[5] with the modification of Kissin[6] and a corrected Q T interval exceeding 0 435 second was considered to be abnormal[7] The QT/TQ ratio was considered to be abnormal if it exceeded the value of 1 with heart rates up to 100 per minute[8,9] The ventricular gradient was calculated after projecting the electrocardiogram with an epidiascope in order to measure the QRS and T complexes[10] A ventricular gradient direction (vector Ĝ) within 30 degrees to the left or right of ÂQRS[11] and a magnitude of 10 to 92 microvolts per second[12] was considered to be normal

All data were submitted to statistical evaluation A probability of 5 per cent was accepted as being significant

Results

1 Body temperatures (Tables II and III) After the experiment the changes in body temperature showed an inverse correlation to the degree of hydration

2 Heart rate

A WORKING EXPERIMENTS (TABLE IV) In subjects on the morning shift the heart rate increased after work This increase was marked in the groups with Restricted W I both in Sodom and Timna workers With Forced W I the heart rate remained unchanged In subjects on the afternoon and night shifts the heart rate after work remained practically unchanged

B WALKING EXPERIMENTS (TABLE V) In order to separate the effect of hydration from the effect of environmental temperature per se the results were grouped and compared according to the environmental temperature After the same effort at the same environmental temperature but at different degrees of hydration the No W I groups had the highest rise in heart rate The heart rate after walking in these latter groups was always significantly higher than in the Forced W I groups

Comment Even in fully acclimatized people there is a tendency for the heart rate to rise with an increase in ambient temperature After physical effort the Restricted W I groups at work and the No W I groups during walking had the highest rises in heart rate which shows clearly the correlation between the state of hydration and the heart rate The lack of increase in heart rate after work in subjects on the afternoon shifts even in the Restricted W I group can be explained by the fact that the last 3 to 4 hours of work on this shift were performed at a much lower ambient temperature

3 QT/TQ ratio

A WORKING EXPERIMENTS (TABLE VI) In Sodom and in Timna after the experiments a prolongation of the QT TQ ratio in workers on the morning shift especially in the Restricted W I groups was observed No significant changes were seen in workers on the afternoon and night shifts

B WALKING EXPERIMENTS (TABLE VII) Before the experiments the QT TQ ratio showed progressive increases with higher ambient temperature After the hike the QT/TQ ratio increased especially in the group with No W I and exceeded the upper normal limit of 1 the increase paralleled the rise in ambient temperature and showed inverse correlation to the conditions of hydration

Comment With higher ambient temperature higher QT TQ ratio were observed even before the experiments After the walking experiments it increased mostly in the group with No W I and reached values higher than 1

4 Corrected Q T interval The mean value of corrected Q T interval remained

Table II Variations in body temperature and weigh under different conditions of hydration Working experiments

Water intake		Morning shift				Afternoon shift				Night shift			
		No of exper	Δ Weight (Gm)	Body temp (C)		No of expe	Δ Weight (Gm)	Body temp (C)		No of expe	Δ Weight (Gm)	Body temp (C)	
			A	B	A		A	B	A		A	B	A
Sodom													
Restricted	M	14	−1 346	36 7	37 8					4	−1 366	37 5	37 4
	SD			0 30	0 35							0 28	0 2
Free	M	56	+250	36 ?	37 6					14	+141	37 2	3 3
	SD			0 60	0 48							0 19	0 18
Restricted vs Free	p			NS	NS							NS	NS
Timna													
Restricted	M	35	−1 553	36 6	37 9	8	−638	37 2	37 1				
	SD			0 34	0 45			0 30	0 5?				
Free	M	37	+700	36 8	37 5	7	+1 072	37 4	36 9				
	SD			0 28	0 17			0 23	0 ?6				
Forced	M	10	+716	36 5	37 3	4	+1 901	37 1	36 9				
	SD			0 3	0 18			0 15	0 53				
Restricted Free	p			0 05	0 001			NS	NS				
Free vs Forced	p			0 05	0 0			NS	NS				
Restricted vs Forced	p			NS	0 001			NS	0 0				

M Mean, SD Standard deviation, p Probability, NS Not significant, B Before experiment, A After experiment

within normal limits in all groups After the experiments the changes in corrected Q T interval were similar to those of the QT/TQ ratio

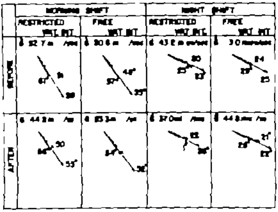


Fig 1 Ventricular gradient before and after working experiments under different condition of hydration in Sodom

5 *Frontal P axis* The mean value of the P axis remained within normal limits in all groups before and after the experiments

A WORKING EXPERIMENTS In the Sodom workers the axis of P deviated to the right, especially in the Restricted W I groups In the Timna workers the axis of P deviated to the right in the Restricted W I group and to the left in the Free and Forced W I groups In the subjects on the afternoon and night shifts the same tendency although to a lesser degree was observed The shift of the axis to the left was clear in the Forced W I group

B WALKING EXPERIMENTS The axis of P shifted to the right in the No W I and Free W I groups and slightly to the left in the Forced W I groups

Comment The axis of P tended to shift rightward in the Restricted or No W I groups

6 *P R interval* The P R interval remained normal in all subjects and showed no significant variations in the different groups

7 *Frontal QRS axis*

A WORKING EXPERIMENTS In the Sodom workers, the mean value of QRS axis remained within normal limits in all groups before and after the experiments (range of −16 to +94 mean of +28 5 to +63 7) The QRS axis remained practically un

Table III Variations in body temperature and weight under different conditions of ambient

Water intake		No of exper	Ambient temp = 34–38°C Δ Weight (Gm) A	Body temp B	A	No of exper	Ambient temp = 38–40 C Δ Weight (Gm) A	Body temp B	A
No W I	M	14	−2 272	37 2	38 4	6	−2 200	37 3	38 8
	SD			1 63	0 71			0 59	0 36
Free W I	M	2	0	36 9	37 2	8	+150	36 9	37 8
	SD			0 1	0			0 22	0 35
Forced W I	M	12	+250	37 2	37 7	7	+167	37 4	37 7
	SD			0 59	0 35			0 22	0 20
No vs Free	p			NS	0 005			NS	0 001
Free vs Forced				NS	0 05			NS	NS
No vs Forced				NS	0 001			NS	>0 001

For key to abbreviations see the footnote to Table II

changed both in the Restricted and Free W I groups In the night workers after the experiment the axis shifted mainly to the left (Δ = 7 2 per cent) in the Restricted W I groups and mainly to the right in the Free W I group (Δ = 15 per cent) In the Timna workers the QRS axis shifted to the left both in the Restricted and the Free W I groups and to the right in the Forced W I group In the afternoon workers the shifts in axis were mainly to the right

B WALKING EXPERIMENTS The axis deviated to the right at lower temperatures and to the left at higher temperatures in the groups of subjects who walked without intake of water In the Free and Forced W I groups an opposite variation was seen

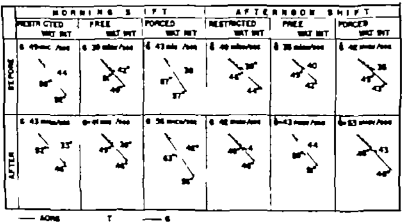


Fig 2 Ventricular gradient before and after working experiments under different condition of hydration in Timna

Temperature and hydration Walking experiments

No of exper	Ambient temp = 40–43 C Δ Weight (Gm) A	Body temp B	Body temp A	No of exper	Ambient temp = 45–47 C Δ Weight (Gm) A	Body temp B	Body temp A
7	−2 312	37 3 0 74	38 7 0 71	5	−2 880	37 4 0 10	39 6 0 44
4	−800	37 4 0 20	37 8 0 14	4	−1 375	37 4 0 14	38 4 0 37
3	+700	37 5 0 32	37 8 0 41	4	+15	37 4 0 71	38 3 0 33
		NS NS NS	0 01 NS 0 01			NS NS NS	0 001 NS 0 001

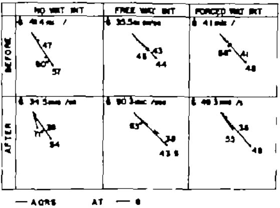
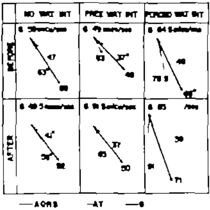


Fig 3 Ventricular gradient before and after walking experiment under different conditions of hydration at a temperature of 36 38 C in Timna



4 Ventricular gradient before and after walking riment under different conditions of hydration at a temperature of 38 40 C in Timna

8 Frontal T axis and S T segment The mean values of the T axis remained within normal limits in all groups

A WORKING EXPERIMENTS After work in the morning the T axis shifted to the left both in the Sodom and in the Timna subjects Only in the Forced W I groups was a shift to the right observed In the afternoon and night workers the T axis of all groups shifted to the right

B WALKING EXPERIMENTS The T axis shifted slightly to the left both in the No W I and in the Free W I groups and to the right in the Forced W I groups

The S T changes were not significant in any of the groups concerned

9 Ventricular gradient (Figs 1 to 6) The mean values of direction and magnitude of the ventricular gradient remained within normal limits both before and after the experiments

I DIRECTION In the working experiments in Sodom (Fig 1) the ventricular gradient shifted to the left both in Restricted W I and in Free W I groups of workers on the morning shift In Timna (Fig 2) in the morning workers the ventricular gradient shifted to the left in the Restricted W I group did less so in the Free W I group and remained practically unchanged in the Forced W I group In the afternoon workers the ventricular gradient shifted mainly to the right especially in the Free W I group

In the walking experiments the ventricular gradient shifted to the left in the

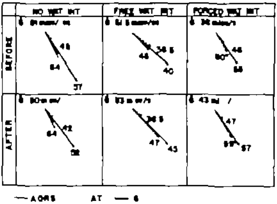


Fig 5 Ventricular gradient before and after walking experiment under different conditions of hydration at a temperature of 40 43 C in Sodom

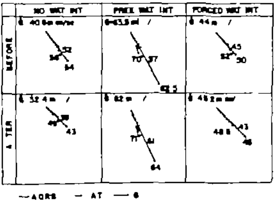


Fig 6 Ventricular gradient before and after walking experiment under different conditions of hydration at a temperature of 45-47 C in Timna

Table IV Variations in heart rate under different conditions of hydration Working experiments

Water intake		Heart rate—Morning shift No of exper	B	A	Heart rate—Afternoon shift No of exper	B	A	Heart rate—Night shift No of exper	B	A
Sodom										
Restricted	M	14	61.6	71.8				4	80.0	79.6
	SD		6.69	9.52					8.04	7.13
Free	M	36	61.8	69.5				55	70.1	72.6
	SD		9.27	10.32					6.59	6.69
Restricted vs Free	p		NS	NS					NS	0.01
Timna										
Restricted	M	33	67.1	74.6	8	69	68			
	SD		10.0	12.5		8.59	12.7			
Free	M	37	65	72	7	69.8	70.3			
	SD		10.2	13.3		11.9	10.5			
Forced	M	10	63	60	4	65	64			
	SD		9.65	9.64		5.44	7.59			
Restricted vs Free	p		NS	0.005		NS	NS			
Free vs Forced	p		NS	0.005		NS	NS			
Restricted vs Forced	p		NS	>0.005		NS	0.05			

For key ... abbreviations see footnote to Table II

No W I groups This shift was more marked with higher ambient temperatures (Figs 3 6)

VENTRICULAR GRADIENT MAGNITUDE In the working experiments (Figs 1 and 2) in Sodom the ventricular gradient decreased after the experiments in the Restricted W I groups whereas it increased slightly in the Free W I groups In Timna the same changes in the ventricular gradient were observed and were more marked in the Forced W I groups These changes were statistically significant

In the walking experiments (Figs 3 6) the ventricular gradient in the same ambient temperature diminished in the No W I groups whereas it increased progressively from the Free to Forced W I groups With higher ambient temperatures a progressive decrease in the ventricular gradient was observed in the No W I groups On the other hand there was an inverse relationship between the increase in the magnitude of the ventricular gradient in the Free and Forced W I groups and the rise in ambient temperature

The magnitude of the ventricular gradient was significantly larger after the experiments with forced intake of water than it was with no intake of water at all ambient temperatures

Repeated experiments

Working experiments (*Table VIII*) In Sodom and in Timna the heart rate as well as the corrected Q T interval were increased There was a decrease in the magnitude of the ventricular gradient in the Restricted W I groups and increase in the Free W I groups

Table V Variations in heart rate under different temperatures and conditions of hydration Walking experiments

Water intake		Heart rate Temp = 36–38 C			Heart rate Temp = 38–40 C			Heart rate Temp = 40–43 C			Heart rate Temp = 45–47 C		
		No of exper	B	A	No of exper	B	A	No of exper	B	A	No of exper	B	A
No W I	M	14	66	100	6	69.5	93.5	7	76	95	5	78	107
	SD		8.04	14.1		5.59	13.3		13	12.2		4.91	10.9
Free W I	M	2	67	70	8	58	68	4	72	86	4	74	91
	SD		2.55	2.55		2.38	2.78		5.05	11.6		4.15	6.38
Forced W I	M	12	64	84	2	72	80	3	75	86	4	85	96
	SD		10.6	10.1		2.55	3.21		12.1	9.14		11.4	3.75
No vs Free	p		NS	0.025 0.01		NS	0.05		NS	NS		NS	0.05 0.025
Free vs Forced	p		NS	0.05 0.025		NS	NS		NS	NS		NS	0.05
No vs Forced	p		NS	0.05 0.025		NS	0.025		NS	0.05		NS	0.025

[illegible]

Walking experiments (Table IX) At an ambient temperature of 36 to 38°C there was a marked increase in heart rate a marked prolongation of the corrected Q T interval and a diminution of the ventricular gradient under restricted intake of water as compared to the changes observed with forced intake of water At an ambient temperature of 45 to 47°C similar but more pronounced changes were observed

Comment The results tend to rule out the influence of individual factors on the electrocardiographic changes observed under various degrees of body hydration and/or ambient temperature

Discussion

The exposure of man to high environmental temperatures is known to produce marked alterations in the circulatory system[18 19] These changes are related mainly to the thermoregulation of the body in conditions of heat stress which require an increased flow of blood to the skin and the onset of active sweating The stroke volume and heart rate increase during exposure to environmental heat even at rest[2 20] Exposure to an environmental temperature of 41°C for a few hours in a reclining position results in an average heart rate of 120 per minute with mild exercise under the same conditions the heart rate may reach 180 per minute[21] In the present studies, even with ambient temperatures reaching up to 47° C the heart rate never attained this degree of tachycardia The lack of expected tachycardia is due to the fact that the subjects studied were permanent inhabitants of hot areas who had been engaged for many years in the same type of work However even in these fully acclimatized subjects the increase in the ambient temperature produced a slight increase in the heart rate at rest (Table V) After the periments all the subjects showed an crease in body temperature and he

rate After the same physical effort performed with restricted or no intake of water the heart rates were observed to be higher than those found under the same ambient temperatures but with free and forced intake of water This shows clearly the effect of different degrees of body hydration on heart rate

The frontal axis of P tends to shift to the right after exercise under normal climatic conditions [3] In the present study a shift to the right was seen mainly in subjects working or walking under restricted intake of water In the others the shift was mainly to the left and may have been due to water repletion of the stomach which prevented a more vertical position of the atrial vector

The corrected Q T interval after physical effort had a tendency to become prolonged in those subjects who performed physical exercise under restricted intake of water and not in the others It is noteworthy that these changes were found between 15 and 30 minutes after the subjects stopped working or walking Since the heart rate remained below 100 in almost all subjects the influence of the heart rate per se on the corrected Q T interval is negligible In order to elucidate this point further a comparison of corrected Q T intervals was made in subjects who showed the same heart rates before and after the experiments This comparison disclosed the same changes in corrected Q T interval as mentioned above namely prolongation in those subjects who performed under restricted intake of water and only slight changes in the others (Table X) Acid base studies determin

Table VI Variations in QT/TQ under different conditions of hydration Working experiments

Water intake		QT/TQ—Morning shift			QT/TQ—Afternoon shift			QT/TQ—Night shift		
		No of exper	B	A	No of exper	B	A	No of exper	B	A
Sodom										
Restricted	M	14	0 593	0 729				4	0 739	0 753
	SD		0 08	0 14					0 03	0 05
Free	M	56	0 606	0 693				14	0 668	0 714
	SD		0 12	0 15					0 08	0 12
Restricted vs Free	p		NS	NS					NS	NS
Timna										
Restricted	M	35	0 625	0 745	8	0 709	0 697			
	SD		0 15	0 15		0 15	0 11			
Free	M	47	0 664	0 740		0 735	0 743			
	SD		0 13	0 19		0 11	0 15			
Forced	M	10	0 588	0 667	4	0 629	0 633			
	SD		0 09	0 10		0 09	0 06			
Restricted vs Free	p		NS	NS		NS	NS			
Free vs Forced	p		NS	NS		NS	NS			
Restricted vs Forced	p		NS	0 05		NS	NS			

[illegible] Table II

Table VII Variations in QT/TQ under different temperatures and conditions of hydration Walking experiments

Water intake		QT/TQ Temp = 36–38 C			QT/TQ Temp = 38–40 C			QT/TQ Temp = 40–43 C			QT/TQ Temp = 45–47 C		
		No of exper	B	A	No of exper	B	A	No of exper	B	A	No of exper	B	A
No W I	M	14	0.667	1.080	6	0.681	1.059	7	0.823	1.066	5	0.827	1.157
	SD		0.07	0.29		0.06	0.20		0.17	0.18		0.11	0.12
Free W I	M	2	0.675	0.677	8	0.542	0.690	4	0.775	0.953	4	0.771	0.940
	SD		0.02	0.10		0.03	0.17		0.10	0.18		0.07	0.17
Forced W I	M	12	0.695	0.756	2	0.750	0.794	3	0.820	0.965	4	0.907	0.992
	SD		0.13	0.15		0.07	0.10		0.12	0.08		0.13	0.16
No vs Free			NS	0.025		0.01	0.02		NS	NS		NS	NS
Free vs Forced	p		NS	NS		0.01	NS		NS	NS		NS	NS
No vs Forced			NS	0.001		NS	0.025		NS	0.05		NS	0.05

For key to abbreviations see Table II

tions of potassium and calcium in the plasma did not reveal overt metabolic factors which could explain the prolongation of the corrected QT interval [34]

Yu has shown that in normal subjects under normal climatic conditions the corrected QT interval shortens in the immediate recovery period after exercise and is prolonged in those suffering from atherosclerotic heart disease Since the coronary blood flow occurs mostly during diastole [37] prolongation of the QT interval with the correspondingly shortened diastolic filling time could explain the cardiac pain experienced by some of Yu's atherosclerotic subjects In the present experiments the diastolic filling time for a given heart rate is shorter in those subjects working or walking under the condition of a restricted intake of water This would imply that in subjects performing physical effort under restricted intake of water some degree of transient relative coronary insufficiency may take place The same comments pertain to the prolongation of the QT/TQ ratio observed by Yu[33] on subjects with atherosclerotic heart disease and on our subjects performing under restricted intake of water

The usual response of the frontal QRS and T axes to exercise under normal climatic conditions is a shift to the right rarely a shift to the left [33] No definite trend in the QRS or T axis could be seen after the experiments described

Since the ventricular gradient represents the resultant of the QRS and T vectors study of it was believed to give a better idea of the state of the myocardium than would the separate changes in QRS and T vectors In our subjects the shifts in the direction of the ventricular gradient after working or walking were small and remained bound to the shifts in the QRS axis The changes in the magnitude of the ventricular gradient remained within the limits of normal however there was a definite trend of the magnitude of the ventricular gradient to diminish progressively with the increase in ambient temperature and the increase in the degree of dehydration

The causes for the decrease in the ventricular gradient in subjects performing

physical exercise in high ambient temperatures and presenting signs of dehydration are numerous and their effect may be complementary increase in body temperature [3] increase in heart rate decrease in cardiac output [3,38] decrease in blood pressure changes in blood pH[34] or plasma potassium [4] and changes in position of the heart [3,38]

In the present study the increase in heart rate was *not* the decisive factor since with the same increase in heart rate there was a progressive decrease in the ventricular gradient from forced to free to restricted intake of water (Table X) There was also no correlation between the per cent increase in the heart rate and the per cent decrease in the ventricular gradient (Tables VIII and IX) Similar lack of correlation between increase in heart rate and decrease in ventricular gradient was described by others during periods of *induced heat in man* [31]

The changes in blood pressure after the experiments were slight and blood pH and plasma potassium remained within normal limits No marked changes in the position of the heart were observed

The common denominators of the subjects *who showed a decrease in the ventricular gradient* after daily work or walking were a decrease in body weight and an increase in body temperature The higher body temperatures observed in these subjects due to their state of dehydration were associated with a more *marked vasodilatation in the cutaneous* vascular bed and a shift of large amounts of blood to the periphery This might have caused a decreased venous return[3] and a diminution in the ventricular gradient by a decrease in the stroke volume [3,38] and/or volume conductor

At high ambient temperatures with insufficient hydration the temperature of the blood in the left ventricle is elevated thereby causing a decrease in the temperature gradient between the myocardium and the blood This might have also been a factor contributing to the changes observed in the ventricular gradient [33]

An increased frontal QRS T angle and

Table VIII Repeated working experiments Morning shift Variations in heart rate corrected Q T (Q T) and ventricular gradient magnitude under different conditions of hydration

Water intake	No of subjects	Heart rate		Q T		Ventricular gradient magnitude	
		B	Δ 1 (%)	*B*	Δ t (%)	*B*	Δ *A* (%)
Sodom							
Restricted		M 61	+16 3	0 36?	+4 6	52 9	−10 3
	12	R 51–73		0 335–0 410		17–80	
Free		M 58 1	+27 3	0 360	+6 9	53 8	+19 5
		R 46–78		0 315–0 425		70–103	
Timna							
Restricted		M 64 3	+19 4	0 410	+7 1	45 9	−12 9
	29	R 37–84		0 320–0 425		38–84	
Free		M 67 6	+9 9	0 350	+1 3	39 0	+7 4
		R 37–90		0 340–0 420		15–65	

R Range [illegible] T [illegible] II

Table IX. Repeated walking experiments. Variations in heart rate, corrected Q-T (Q-Tc), and ventricular gradient magnitude under different temperatures and conditions of hydration

Ambient temp. (°C)	Water intake	No. of subjects	Heart rate B	Heart rate Δ A (%)	Q-Tc B	Q-Tc Δ A (%)	Ventricular gradient magnitude B	Ventricular gradient magnitude Δ A (%)
36-38	No W. I.	6	M 64.5	+46	0.393	+7	40.5	−11
			R 57-68		0.355-0.420		19-66	
	Forced W. I.		M 65.8	+28	0.372	−3	48.5	−4
			R 62-69		0.310-0.430		34-68	
45-47	No W. I.	4	M 77	+41	0.407	+3	43.5	−25
			R 72-86		0.385-0.450		31-56	
	Forced W. I.		M 85	+13	0.396	−2	44	+2.7
			R 70-107		0.355-0.420		21-66	

R, Range. For key to other abbreviations see the footnote to Table II.

Table X. Changes in corrected Q-T (Q-Tc) and ventricular gradient magnitude under different conditions of hydration in subjects having similar heart rates

Water intake	No. of subjects	Heart rate B	Heart rate Δ A	Q-Tc Δ A (%)	Ventricular gradient magnitude Δ A (%)
Restricted	4	65	−5	+1.8	−20.9
Free	5			+0.5	+29.9
Restricted	2	55	+5	+7.8	−38.0
Free	5			−0.6	+16.5
Forced	2			−0.3	+32.9
Restricted	3	50	+10	+2.1	−12.0
Free	2			−1.6	+31.3
Restricted	3	70	+10	+12.0	−9.6
Free	2			+4.6	+31.9
Restricted	9	60	+20	+18.7	−18.3
Free	3			+3.2	+4.5

For key to abbreviations see footnote to Table II.

hence a decrease in the ventricular gradient in healthy man after strenuous exercise has been reported and attributed to left ventricular ischemia[14] In this study an increase in the QRS-T angle and decrease in the ventricular gradient was observed in subjects working or walking with restricted or no intake of water It stands to reason therefore that these changes may have been related to the transient relative coronary insufficiency described in connection with the changes seen in the QT/TQ ratio and the corrected Q T interval The fact that with overhydration these changes are prevented or reversed favors the assumption that they are secondary to dehydration

It is difficult to assess the long term prognostic significance of the relatively slight changes seen in the QT/TQ ratio the corrected Q T interval and the magnitude of the ventricular gradient which were observed during several consecutive summers in the same subjects Further studies in populations living permanently in hot areas are needed in order to elucidate this point

Summary

Electrocardiographic changes seen during daily work or after a hike under different conditions of hydration in young and healthy permanent residents of hot areas on 189 working days and in 71 walking experiments are described

Even at rest there was a slight increase in heart rate which paralleled the rise in ambient temperatures The rise in heart rate after daily work or after 2 hours of walking was most marked in subjects under a restricted intake of water was less marked in subjects under free intake of water and was least marked in those under forced intake of water

An increase in the QT/TQ ratio prolongation of the corrected Q T interval and a decrease in the magnitude of the ventricular gradient were observed in subjects working or walking under restricted intake of water These changes were less marked in subjects under free intake of water and were least marked in those under forced intake of water independent of the changes in heart rate

The possibility that the electrocardiographic changes observed can be related to the decrease in the venous return as a result of dehydration and/or to a transient relative coronary insufficiency is discussed

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Triamterene

Clinical studies in arterial hypertension

*Yves Morin, M.D.**
*Louise Turmel, M.D.**
Jean Fortier, Ph.D.
Quebec, Canada

Triamterene,† a triaminopteridine, was thought to be an inhibitor of aldosterone in experimental animals[1] and clinically.[2] Indeed, like spironolactone, it prevents the retention of sodium and loss of potassium induced by various mineralocorticoids. However, given to adrenalectomized dogs, triamterene increases the output of sodium.[3] The frequent dissociation between the excretion of sodium and the reabsorption of potassium[4] suggests that triamterene may interfere with tubular reabsorption of sodium by a mechanism other than cation exchange.

The following report presents the results of our studies on the relative activity, toxicity, and frequency of side effects with the chronic oral administration of triamterene in man.

Method of investigation. Forty-five outpatients who were suffering from arterial hypertension were selected for this study, but only 30 patients remained in the study until it was completed. Average blood pressures before treatment were 208/125 and 194/104 mm. Hg, respectively, for male and female patients. According to Keith and Wagener's classification,[5] 15 patients had Grade I hypertension, 12 had Grade II, and 3 had Grade III. The patients were seen on a weekly basis 2 hours after taking their medication. Blood pressure was measured by two observers with the patients in both the standing and the supine positions.

Triamterene (37.5 mg. four times daily) was compared to hydrochlorothiazide (10 mg. four times daily). Each drug was administered during 4 weeks on a double-blind basis, and the order in which a given patient received the various drugs was randomized.

The average values of systolic and diastolic readings for each treatment period were computed. We compared the differences in these average values and submitted these differences to the sign test, thus indicating whether the direction of change was significant at 5 per cent level.

The cardiac output was determined by the dilution principle according to a method that we have previously described. Blood volume was determined by chromium 51 tagged red cells.[7] Renal clearance of para-aminohippuric acid was performed according to Hamburger's method,[8] except that urethral catheterization was not carried out in any of the subjects with normal renal function.

Four patients who were suffering from

From the Hôtel-Dieu Hospital, Quebec, and the Department of Medicine, Laval University Medical School, Quebec, Que., Canada.
Received for publication May 4, 1964.
Address: Hôtel-Dieu, Québec, 11 Charlevoix, Québec 4, Québec, Canada.
*Fellow, Medical Research Council.
†Kindly supplied by Dr. J. Weyman of Smith Kline & French Laboratories. DYTAC

Table I. Effect on blood pressure of triamterene and hydrochlorothiazide

Treatment	Mean value (± one standard deviation)
Standing position	
Triamterene	177 (±5) / 102 (±3)
Hydrochlorothiazide	167 (±5) / 98 (±3)
Supine	
Triamterene	175 (±5) / 99 (±2)
Hydrochlorothiazide	168 (±5) / 96 (±3)

essential hypertension were selected for these hemodynamic studies which lasted 4 weeks. During the second and the third weeks of this study, the patients received triamterene, 37.5 mg. four times daily. Measurements of blood pressure, blood volume, cardiac output, renal plasma flow, and salivary Na/K ratio were performed on a weekly basis. The sodium/potassium ratios of saliva were determined according to the methods of Gibson.[9] Patients placed on metabolic balance studies received a fixed diet that contained 130 mEq. of sodium and 40 mEq. of potassium daily; the electrolyte content of foodstuff was not, however, chemically determined.

Antihypertensive effect of triamterene. The antihypertensive effect of triamterene was first demonstrated by Crosley. Table I illustrates the hypotensive effect of triamterene as compared to that of hydrochlorothiazide. It can be seen that hydrochlorothiazide is more potent than triamterene. The difference between the means is not statistically significant, but the direction of this change, as determined by the sign test, is significant at a 5 per cent level. It should be pointed out that hydrochlorothiazide was given at a dosage of 40 mg. daily, a dosage situated in the lower part of the sigmoidal dose-response curve, whereas the dose of triamterene (150 mg. daily) lies near the top of the same curve.

It can be concluded that triamterene is a weak antihypertensive agent and that it has no advantage over the thiazide derivatives in this respect. The same conclusion was reached in a recently published study by Heath and Freis.[10]

Hemodynamic effects of triamterene. Because triamterene has little effect on blood pressure, it cannot be expected to determine important hemodynamic disturbances.

It can be seen from Table II that the administration of 150 mg. of triamterene daily results in a small contraction in blood volume, a small drop in cardiac output, and a very slight increase in total peripheral resistance. In acute studies, however, Rowe[11] found that after intravenous administration of triamterene there was a significant decrease in cardiac output in association with a 19 per cent increase in total peripheral resistance. This suggests a type of antihypertensive action similar to that of chlorothiazide. What happens after more prolonged administration has not been determined.

It may also be seen in Table II that in 2 patients a sharp rise in cardiac output with little change in blood pressure occurred after 2 weeks of treatment. This finding is at present unexplained.

The administration of triamterene reduces the glomerular filtration rate.[1] It will be seen from Table II that triamterene, 150 mg. daily, also caused a decrease in the renal plasma flow of the 4 patients under investigation. This reduction in effective renal arterial circulation was due mainly to the contraction of blood volume and to the drop in cardiac output. However, a direct action of the drug in redistributing renal blood flow within the kidney remains a possibility.

Electrolyte balance studies. Electrolyte balance studies were performed in nonedematous hypertensive subjects according to the ABBA method of Gold.[12] It will be seen in Fig. 1 that, as would be expected, both triamterene and hydrochlorothiazide exhibit, with time, decreasing natriuretic activity, whereas their effect on the excretion of potassium remains stable throughout the period of study. However, hydrochlorothiazide (in the low dosage used, 40

mg daily) produces consistently greater natriuresis than does triamterene (in the optimum dosage of 150 mg daily) Triamterene is therefore a mild natriuretic agent Fig 1 also shows the proportionally much greater difference in the excretion of potassium induced by both drugs This marked potassium saving property of triamterene is the most remarkable effect of the drug

In our hands it has rapidly normalized the hypokalemia commonly induced by thiazides and this rapidity of action has suggested to [illegible]nchini[11] that triamterene in addition to its renal potassium sparing effect may somehow modify the general distribution of potassium in the body

This effect also suggested the possibility that the chronic administration of triamterene might lead to abnormally high and toxic levels of serum potassium Therefore we administered triamterene 200 mg daily to 8 subjects for a period of 130 days It will be seen from Table III that although there is a small increase in serum potassium after 5 days the subsequent

Table II

Weeks	*Treatment*	*Mean BP* (mm Hg)	*Blood volume* (L)	*Cardiac output* (L per min)	*Peripheral resistance* (mm Hg/ cc/min)	*Renal plasma flow* (cc/min)	*Salivary ratio* (Na/K)
Case 1							
A	0	126	4.6	8.3	15.2	531.0	2.54
B	Triamterene	120	4.08	6.1	19.7	334.0	1.96
C	Triamterene	118	4.17	4.4	26.8	434.0	1.69
D	0	130	3.76	4.3	30.2	470.2	1.81
Case 2							
A	0	150	4.15	9.3	17.2	405.4	1.50
B	Triamterene	136	3.46	6.5	20.9	445.4	1.56
C	Triamterene	135	3.61	8.8	15.3	257.0	1.40
D	0	140	3.65	6.9	20.3	455.0	1.77
Case 3							
A	0	125	4.17	7.4	17.3	578.0	1.45
B	Triamterene	126	3.90	6.3	20.0	391.0	1.37
C	Triamterene	135	3.61	5.3	25.1	393.0	1.29
D	0	142	3.40	4.9	28.8	427.0	1.30
Case 4							
A	0	146	3.54	5.0	29.2	523.7	1.57
B	Triamterene	146	3.53	4.8	30.4	459.0	1.09
C	Triamterene	143	3.38	5.7	25.1	300.3	0.70
D	0	[illegible]	3.42	4.7	32.3	515.0	1.03
Average							
A	0	137.50	4.1[illegible]	[illegible].50	19.73	498.78	1.75
B	Triamterene	132	3.74	5.93	22.75	40[illegible].45	1.50
C	Triamterene	13[illegible].25	3.69	6.05	23.08	344.83	1.27
D	0	140.75	3.56	5.70	27.90	416.80	1.48

Table III *Serum potassium (mEq/L) in 8 patients treated with triamterene 200 mg daily*

	Days								
	0	*5*	*15*	*25*	*35*	*50*	*65*	*100*	*130*
Average ±S D	4.65 ±0.47	4.99 ±0.41	4.78 ±0.33	4.69 ±0.34	4.[illegible]8 ±0.55	5.13 ±0.17	5.12 ±0.33	5.07 ±0.3[illegible]	4.59 ±0.39

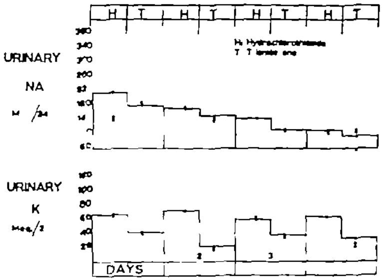


Fig. 1. Electrolyte excretion after the administration of hydrochlorothiazide and triamterene. Three patients received hydrochlorothiazide during the first and fourth days of the study and triamterene on the second and third day. Three other subjects received the same drugs, triamterene on the first and fourth day, and hydrochlorothiazide on the second and third day of the study.

values are well within normal limits (the correlation coefficient between serum potassium levels and time being 0.002).

It has now been shown that triamterene brings about a contraction of blood volume, some loss of sodium, and an elevation of serum potassium, three phenomena that, according to Genest[14] stimulate directly or indirectly the secretion of aldosterone. It will be seen in Table II that while under treatment all 4 patients showed a drop in their salivary Na/K ratio which probably indicates increased mineralocorticoid activity (although we cannot rule out a direct action of triamterene on the salivary glands).

In view of this evidence we believe that the main limiting factor of triamterene-induced natriuresis and the potassium-sparing effect is the state of secondary hyperaldosteronism brought on by the drug.

Side effects and toxicity. The side effects of triamterene were compared to those of hydrochlorothiazide on a double blind basis in 26 patients. The ratio of the sum of complaints experienced by those taking triamterene to the sum of complaints by those on hydrochlorothiazide was 0.91. The only side effect that could be specifically attributed to triamterene was mild diarrhea.

Twenty-eight patients received triamterene for an average of 5 weeks. The following laboratory tests were performed regularly and were all found to be within normal limits: nonprotein nitrogen, serum glutamic pyruvic transaminase, and cephalin-cholesterol flocculation tests. To 4 diabetic otherwise untreated patients triamterene (200 mg. daily) was administered for 1 week; fasting blood sugars showed no significant change during this period. Triamterene was also given to 6 gouty subjects for a period of 130 days; serum uric acid levels remained constant.

Summary and conclusions

Triamterene was found to have mild hypotensive and natriuretic properties. The most striking effect of this new agent was that of potassium sparing. Triamterene was found not to induce various deleterious metabolic effects induced by the thiazide derivatives.

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Beriberi heart disease

Physiologic data and difficulties in diagnosis

*Philip I. Wagner, M.D.**
Portland, Ore.

A recent experience in our hospital has pointed up the problems encompassed in making a diagnosis of beriberi heart disease.

The disease itself is relatively rarely reported in this country. Blankenhorn,[1] using broad diagnostic criteria, reported an incidence of 0.1 per cent of all medical admissions to Cincinnati General Hospital. Most recent publications contain only case presentations. Hence, because of the rarity of the disease, the index of suspicion is not high.

The problem is further compounded by varying diagnostic criteria and varying descriptions of the clinical syndrome found in the literature. Such terms as *wet* and *dry*, *Oriental* and *Occidental*, *pernicious*, and *shoshin* lead one to believe that there are many clinical situations and perhaps diseases caused by this single entity of thiamine deficiency. This communication attempts to bring together the various descriptions and to propose definitive diagnostic criteria for beriberi heart disease.

The clinical picture of beriberi heart disease was first reported in the early nineteen hundreds by Oriental physicians. It was brought to the attention of Western physicians in 1929 by Aalsmeer and Wenckebach[2] and in 1930 by Keefer,[3] both of whom described the disease as seen in the Orient. The former, in Java, depicted the disease as involving primarily the right side of the heart and being basically hyperkinetic in nature, with pistol-shot sounds over the vessels, wide pulse pressures, flushed skin, and rapid circulation. The disease was often fulminant and terminated in sudden vascular collapse and death, a form which had previously been described by Japanese physicians and named by them *shoshin beriberi*. The dry form of beriberi usually followed this course, whereas the wet form had a more gradual onset, with edema, often massive, and symptoms of almost pure right-sided heart failure. Recovery in both forms was usually rapid with bed rest and an adequate diet. The authors were amazed by the minimal amount of peripheral neuritis and the lack of electrocardiographic changes seen in both varieties of patients. Keefer[3] in China found the disease to be quite similar, with the early symptoms basically those of right-sided heart failure, but often also including symptoms of orthopnea and dyspnea. He found the cardiac impulse feeble and diffuse and observed no hyperdynamics of the heart with fluoroscopy. In his series, the pulse pressures before and after recovery were not significantly different. He also observed the lack of peripheral neuritis in the patient with cardiac beriberi and noted that people with severe neuritis rarely developed symp-

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*Resident in Cardiology, Veterans Administration Hospital and the University of Oregon Medical School, Portland, Ore. Present address: United States Naval Hospital, San Diego, Calif.

toms of heart disease. This and the finding that heart manifestations occurred predominantly in individuals doing strenuous labor caused him to postulate that the cardiac form occurred in people with a need for high carbohydrate energy, whereas sedentary patients, such as those crippled with neuritis, were spared cardiac involvement. Both sets of authors found that the disease was aggravated by exercise and improved by bed rest alone.

The disease and its cardiovascular manifestations were also reported early in this hemisphere by Kepler[2] in 1925 and by Scott and Hermann[3] in 1928. Both found the condition to be similar to that seen in the Orient and caused by the same dietary deficiency.

In 1937, Weiss and Wilkins[4] pointed out that in their series of 120 patients with beriberi a large percentage were alcoholics or drug addicts. They found symptoms of left heart failure in conjunction with the right heart failure more often than did Aalsmeer and Wenckebach. They also observed that a higher percentage of the patients had peripheral neuritis and lacked a history of strenuous work. Other than these differences, they found that in Philadelphia there was little difference between Occidental Oriental alcoholic and dietary-deficiency beriberi.

In 1945, Blankenhorn[5] advanced his opinion that many cases of beriberi heart disease were being overlooked because of adherence to the concept of the disease as seen in the Orient. Furthermore, it was his opinion that the Occidental disease could be different than the Oriental form. Therefore, he promulgated the following criteria for diagnosis: (1) enlarged heart with a normal sinus rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral neuritis or pellagra, (5) nonspecific ST-T changes on the electrocardiogram, (6) no other cause evident, (7) dietary deficiency for at least 3 months, (8) response to thiamine or autopsy evidence.

Of the foregoing criteria, only numbers 4 and 8 make a positive diagnostic proposal. Peripheral neuritis is often found *in* alcoholics who do not have beriberi heart disease. Response to thiamine, unless dramatic and to this agent alone, can be easily confused with bed rest, other cardiotonic drugs and regimens, and the natural course of a disease. Furthermore, no publication has been made of any pathologic findings at necropsy in patients with beriberi that are not found in other degenerative diseases and other forms of heart failure.[6]

After the publication of Blankenhorn's criteria, several articles appeared in the literature describing pulmonary embolization,[7] cardiac hypertrophy and mural thrombosis,[8] chronic relapsing heart failure in spite of thiamine therapy, and cardiac insufficiency,[9,10] all presumably due to beriberi heart disease. One recent article presents 12 autopsied cases in which the diagnosis was made on lack of other etiology and hydropic degeneration of the myocardial cells.

In 1947, the first physiologic study of a patient with beriberi heart disease was published by Burwell and Dexter.[1] Since that time, 12 more cases have been reported for which there were varying amounts of hemodynamic data. These have been tabulated in Table II and are discussed along with this additional case report.

Case report

J. W., a 36-year-old male wood worker, entered the Portland Veterans Administration Hospital on March 8, 1961, because of marked edema. He first noted intermittent swelling of the ankles about 1 year prior to admission. This gradually progressed to massive edema of the legs and abdomen, but there was no orthopnea, paroxysmal nocturnal dyspnea, or dyspnea on exertion. He denied alcoholism and stated that he ate a small but balanced diet. He continued to work until 1 week prior to admission in spite of his edema. Physical examination revealed a temperature 99.4 F., pulse of 120, and blood pressure of 118/70 mm. Hg. The patient was pale, slightly icteric, and able to lie comfortably flat in bed. There was massive dependent edema to the costal margin. No spider angiomata were seen on the skin. The neck veins were distended to the angle of the jaw when he was in the sitting position, and both [illegible] and [illegible] waves were easily visible. The lungs were clear. The precordium showed no heave, overactive apical impulse, or abnormal thoracic movement. There was a regular tachycardia and a mid-diastolic gallop, and some observers heard a pericardial click. There was a Grade [illegible]/6 systolic ejection murmur at the base. The second sound split physiologically. The abdomen was distended with fluid, but the liver could be palpated 5 cm. below the right costal margin. The spleen was not palpable. Arterial pulses seemed to be equal in all extremities and showed no abnormal paradoxical

Table I Data obtained at cardiac catheterization

Parameter	Before thiamine		After thiamine	
	Rest	Exercise	Rest	Exercise
Pressures (mm Hg)				
Right atrium				
Mean	9	—	5	—
Pulmonary artery	43/21	53/27	28/12	35/15
Mean	30	34	17	25
Pulmonary capillary				
Mean	13	—	4	—
Brachial artery	170/82	180/90	150/85	185/100
Mean	115	125	105	130
Oxygen uptake (ml /min)	298	474	284	608
A V O difference (volumes)	2 2	3 3	4 1	6 2
Cardiac output (L /min)	13 6	14 4	6 9	9 8
Cardiac index (L /min /M ²)	7 1	7 4	3 8	5 4
Pulmonary vascular resistance (A R U)	176	188	197	204
Peripheral vascular resistance (A P U)	677	694	1 217	1 061

Abbrev res t nce ... qu l d ... m

phasing Neurological examination failed to show any evidence of peripheral neuritis Laboratory data revealed the following white blood count of 5 000 per cubic millimeter with a normal differential hematocrit 30 per cent erythrocyte sedimentation rate 40 mm per hour albumin 3 4 Gm per cent globulin 2 6 Gm per cent SGO T 70 units VDRL nonreactive blood urea nitrogen 7 mg per cent bilirubin 1 8 mg per cent total direct 0 54 mg per cent BSP 32 per cent retention at 30 minutes thymol turbidity 3 units alkaline phosphatase 8 3 King Armstrong units electrolytes in milliequivalents per liter—Na 132 Cl 96 HCO 27 K 3 6 prothrombin and proconvertin activity 50 per cent LF preparation negative PPD intermediate strength negative urinalysis normal Chest x-ray examination showed borderline enlargement of the heart The electrocardiogram showed nonspecific T wave changes Venous pressure was 27 mm of water and circulation time was 13 seconds Cardiac fluoroscopy revealed no specific chamber enlargement and normal dynamics

The patient s therapy for the first 4 days consisted only of bed rest low sodium diet and 2 c c of Mercuhydrin which produced no diuresis On the fourth day he was given a digitalizing dose of digoxin aldactone and multivitamin capsules as well as parenteral vitamin B complex

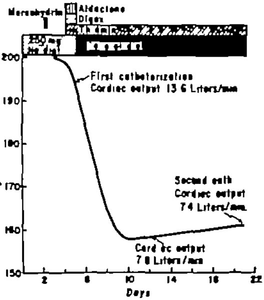


Fig 1 Clinical course and therapy of patient with beriberi heart disease

Because of the quiet and relatively normal sized heart questionable pericardial click nonspecific electrocardiographic changes fever pulsation of the neck veins and lack of other obvious etiology the diagnosis of constrictive pericarditis was entertained On the fifth hospital day right heart catheterization was performed and the results are shown in Table I When the patient s sister with whom he lived was contacted after the catheterization procedure she stated that the patient s diet had consisted of low-cost wine during the past 6 months that he had resided with her After the diagnosis of beriberi heart disease was made all medications except thiamine were stopped and the patient was placed on a general diet It should be noted that the catheterization was performed 12 hours after the patient had received vitamin B complex and that diuresis had already begun It should also be noted that the patient received only a digitalizing dose of rapid acting glycoside The patient s recovery was dramatic and complete with a net diuresis of 40 pounds over a period of 5 days Fig 1

shows the response as measured by changes in weight and the medications in time sequence. A repeat determination of cardiac output by the dye-dilution method was made on the twelfth hospital day. The patient was again catheterized after 16 days of thiamine.

Hemodynamic data

METHODS. Pressures were transduced by the same Statham electric strain gauges at both catheterizations and recorded with a Sanborn 150 direct writing amplifier. Wedge pulmonary capillary pressures had characteristic wave form and were reproducible on both occasions although no blood could be withdrawn. Blood gases for the Fick output determination were analyzed by the Peters and Van Slyke method and the oxygen consumption by the Scholander micro gas analysis of expired air. Evans Blue dye dilution curves were transduced with a Colson densitometer, recorded with a Texas Instrument Servowriter and calculated by the Stewart Hamilton method. Difference between the Fick and dye output determinations was 3.8 per cent. Exercise consisted of alternate leg raising from the supine position for 5 minutes. Vascular resistance was calculated by the drop in mean pressure in a given circuit divided by the cardiac output according to the formula

$$\text{Resistance} = \frac{P_1 - P_2\ (\text{mm Hg}) \times 80}{\text{Cardiac output (liters/minute)}} =$$

dynes sec./cm.

Total pulmonary and total systemic vascular resistance were calculated using zero as the value for P_2.

RESULTS. The data from cardiac catheterization are tabulated in Table I. The mean pulmonary arterial pressure as well as the pulse pressure were found to be elevated at rest. The right atrial pressure was slightly elevated and showed prominent a and v waves that faded with expiration. The pulmonary capillary pressure was borderline increased. The peripheral arterial pulse pressure was elevated and the A-V oxygen difference was abnormally low. The peripheral vascular resistance was markedly decreased and hence the cardiac index was elevated. With exercise the cardiac index was relatively fixed and both the mean pulmonary and peripheral arterial pressures increased slightly.

After 2 weeks of therapy with thiamine there was a complete return to normal parameters of the resting and exercise data except for the slight rise in the pulmonary arterial pressure with exercise. The A-V oxygen difference and the cardiac index were within normal limits. The same value for cardiac output had been obtained 1 week previously by the dye-dilution method indicating that 1 week after thiamine therapy had begun peripheral vascular resistance was already normal.

Discussion

In Table II the existing published cases of beriberi heart disease with objective physiologic data are listed including our case report.[1-13] It is apparent that before treatment the disease was characterized by a high cardiac output which was the

Table II. Physiologic data in published cases of beriberi heart disease

Author		Before thiamine: Cardiac output (L./min.)	Before thiamine: Cardiac index (L./min./M.²)	After thiamine: Cardiac output (L./min.)	After thiamine: Cardiac index (L./min./M.²)	Peripheral vascular resistance (dynes sec. cm.⁻⁵): Before thiamine	Peripheral vascular resistance (dynes sec. cm.⁻⁵): After thiamine
Leonard et al	1	16.3		5.8		400	1,780
Labey et al	2	16.1	7.8	7.8	4.2	497	1,005
Burwell and Dexter[22]	3	11.8		5.3		475	1,253
Wagner	4	13.6	7.1	6.9	3.8	677	1,717
Iseri et al[14]	5	14.4	7.8	10.7	5.8	Low	Normal
Iseri et al	6	11.4	5.8	Normal		Low	Normal
Iseri et al[16]	7	8.3	4	11.2†	6.3	Low	
Blacket	8	17.8†	10.0	7.1	4.0	315	1,240
Blacket	9	19.8	12.0	5.8	3.5	404	1,448
Blacket	10	15.7	8.4	Recovers			
Campbell et al[16]	11		4.3		2.5		
Campbell et al	12		7		2.7		
Olson[13]	13	5.0	10.2				

Calculated from data published.
†A shortened table was ... [illegible]
Calculated using ... from published graph.

result of a low peripheral vascular resistance It is also clear that with the administration of thiamine peripheral vascular resistance returned to normal within a period of 2 to 3 weeks Indeed Lahey[17] was able to show an increase in the peripheral vascular resistance in a period of 60 minutes after the intravenous administration of thiamine

It is also remarkable that these failing hearts were all pumping considerable amounts of blood In 2 cases a cardiac index of 12 was found which would certainly qualify as maximum under extreme stress for a normal heart It would appear legitimate to draw the conclusion as has been done previously[20] that in beriberi heart disease the situation is analogous to a peripheral A V shunt and that heart failure is due to the imposed work load not to any intrinsic lesion of the myocardium itself

All cases in Table II are Occidental alcoholics In none of these cases was residual heart disease reported and indeed in 109 American prisoners-of war who developed beriberi in Japan during World War II long term follow up failed to reveal a significantly higher incidence *of heart disease than in a random sample* of individuals in this age group Furthermore all heart disease in this group with the possible exception of one case could be explained by usual causes

From the foregoing data it would seem *reasonable to conclude that thiamine* deficiency regardless of its geographic location results in one specific disease state The cardiovascular disease in beriberi is the result of the loss of peripheral vascular resistance the mechanism of which is not known The peripheral vascular resistance is restored to normal within a period of 2 weeks specifically by thiamine There may well be subclinical forms of the disease and irreversible damage to the heart by the work load but certainly this still remains to be objectively defined

The only chemical abnormality in the serum that has been demonstrated reasonably consistently in beriberi is an increase in carbonyl compounds reported as pyruvic acid or bisulfite binding substances They have been reported to be as high as four times normal resting values in fulminating cases of beriberi but in mild cases the levels may be normal[3] Other disease states are known to have high resting levels of pyruvic acid [1]

At the present time in most centers it is possible to easily (and portably) measure the mean arterial and venous pressures and to obtain accurate dye dilution outputs and hence calculate the peripheral vascular resistance An objective diagnosis of beriberi heart disease can be made by the finding of a low peripheral vascular resistance which returns to normal with adequate thiamine therapy It is proposed that diagnostic criteria for beriberi heart disease be divided into presumptive and definitive as follows *Presumptive*—(1) Congestive heart failure with more or less right sided symptoms predominating (2) chronic alcoholism or other cause of dietary deficiency for at least 3 months (3) peripheral neuritis or other evidence of vitamin deficiency (4) evidence of hyperkinetic circulation in the absence of thyrotoxicosis or A V shunt (5) high serum pyruvic acid (bisulfite binding substances) *Definitive*—(1) Abnormally low peripheral vascular resistance with return *to normal within a period of 2 weeks after* adequate thiamine therapy

Summary

A brief history of beriberi heart disease is presented together with a case *report that includes physiologic data be*fore and after recovery from the congestive state The hemodynamic findings are compared with previously reported data all indicating a low peripheral vascular resistance that results in a high cardiac output Presumptive and definitive diagnostic criteria are postulated for the diagnosis of cardiovascular involvement in beriberi

I wish to express my appreciation to Dr Leonard W Ritzmann Section Chief Cardiology Veterans Administration Hospital Portland Ore for his helpful criticism

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Experimental and laboratory reports

Elevation of serum cholesterol after administration of nicotine

*Alfred Kershbaum, M.D.**
*Samuel Bellet, M.D.***
*Rostam Khorsandian, M.D.***
Philadelphia, Pa.

Recent statistical studies have shown an association between cigarette smoking and coronary heart disease[1,2] and between cigarette smoking and elevated serum lipids.[4] To help determine whether a cause and effect relationship is responsible for these associations, experimental studies of the effect of smoking and nicotine on lipid metabolism were undertaken.

Previous observations in our laboratory[7] have shown that free fatty acids are rapidly mobilized after cigarette smoking in man and after the administration of nicotine in dogs. This effect is dependent upon active functioning of the adrenal glands and the sympathetic nervous system and is accompanied by an increase in the secretion of catecholamines.[9] Since the administration of catecholamines in dogs has been found to cause an elevation of lipoprotein lipids in addition to free fatty acids,[10,11] the present study was undertaken to investigate the possibility of a similar effect on lipoprotein lipids after the administration of nicotine.

Methods

Twenty adult healthy mongrel dogs (weight of 10 to 15 kilograms) were used in this study. They were housed indoors in similar individual kennels under similar environmental conditions. Each animal was fed once daily at 9 A.M. The daily ration was the same for all dogs and consisted of the following: Wayne's dry meal dog food (4 large standardized measures), Ken-L Burger dog food (4 large standardized measures), and bone meal (one cup). This mixture supplied 20 per cent protein, 7 per cent fat, 3 per cent fiber, 6.5 per cent ash, and essential minerals and vitamins. Water was given freely. All dogs were weighed weekly before feeding on the same day of the week. They were not permitted outside their kennels except for blood sampling and weighing.

To obtain base-line serum cholesterol and triglyceride levels, fasting venous blood samples were taken daily for 1 week. After this, in 9 dogs, nicotine bitartrate in a slow absorption aqueous vehicle containing 2 per cent glycerin and 2 per cent

From the Division of Cardiology, Philadelphia General Hospital, Philadelphia, Pa.
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*Assistant in Charge, Division of Cardiology, Philadelphia General Hospital.
**Director, Division of Cardiology, Philadelphia General Hospital.
***Research Fellow, Division of Cardiology, Philadelphia General Hospital.

gelatin was given intramuscularly daily before feeding for 6 weeks. A dose of 0.5 mg. per kilogram was given for 4 weeks, then increased to 1.0 mg. per kilogram for 2 weeks. The drug was then withheld and the animals were observed for an additional 2 weeks. In 5 dogs the glycerin gelatin vehicle without nicotine was given daily for 4 weeks. In 6 dogs no injections were given during the 8 week period of the experiment.

Weekly samples of venous blood were drawn before feeding in all animals. Concentrations of serum cholesterol were determined by the method of Abell and associates[12]; levels of serum triglycerides were determined by the method of Van Handel and Zilversmit.[13] All analyses were made in duplicate.

In 5 of the 9 dogs receiving nicotine limb and chest lead electrocardiograms were taken weekly. These animals were sacrificed at the end of the experiment and sections of the aorta and the coronary and femoral arteries were examined grossly and microscopically.

Results

Levels of serum cholesterol in dogs receiving nicotine. Table I shows the cholesterol values in all dogs receiving nicotine. There was a significant elevation of cholesterol in 8 of the 9 animals. The mean cholesterol concentration rose after the first week of nicotine from a pre-nicotine value of 144 ± 11.8 mg. per cent to a peak of 216 ± 15.3 mg. per cent ($p < 0.01$) at the end of the fourth week (50 per cent). The dose of nicotine was then increased to 1.0 mg. per kilogram in order to compensate for drug tolerance. At the end of the fifth and sixth weeks the mean cholesterol values were 201 ± 11.4 mg. per cent ($p < 0.01$) and 200 ± 11.8 mg. per cent ($p < 0.01$), respectively. The drug was then stopped and the cholesterol dropped to 161 ± 13.2 mg. per cent ($p < 0.05$) after 2 weeks. Mean values are shown in Fig. 1.

Levels of serum cholesterol in control dogs. In the control dogs receiving no injections there was no significant change in serum cholesterol during the 8 week period of the experiment. In the control animals receiving injections of the glycerin gelatin vehicle which contained no nicotine there

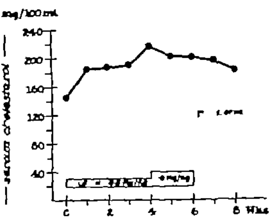


Fig. 1. Mean cholesterol level in dogs given daily injections intramuscularly of nicotine bitartrate in a slow absorption vehicle.

was likewise no significant effect on the levels of cholesterol (Table II).

Levels of serum triglycerides in dogs receiving nicotine. Mean serum triglyceride values are shown in Table III. There was no significant change in the levels of triglycerides during the administration of nicotine; control dogs also showed no change.

There was no notable change in weight or feeding habits of the dogs in the nicotine or control groups. In the dogs in which these studies were made no electrocardiographic abnormalities were noted and no pathologic changes were found in the aorta or the coronary or femoral vessels.

Discussion

The dogs in these experiments showed a significant hypercholesteremic response to nicotine. In rabbits Wenzel and Beckloff[14] previously demonstrated elevated plasma cholesterol after oral nicotine and Maslova[15] reported a similar effect after nicotine by injection. However, Wenzel and associates[16] found no added effect on plasma cholesterol after nicotine in rabbits which were fed an atherogenic cholesterol supplement (1.0 per cent). In our experiments no cholesterol was added to the ration and both the nicotine and control dogs received the same diet.

The administration of nicotine in a slow absorption vehicle was resorted to for two reasons. First, in our preliminary experiments[7] nicotine bitartrate in a buffered saline vehicle was given intramuscularly

4 times daily in 8 dogs in doses up to 1.0 mg. per kilogram with no effect on serum cholesterol. The same nicotine solution was then given by continuous intravenous infusion for 4 hours daily in a dose of 10 μGm per minute per kilogram. Five of 13 dogs showed a significant rise in cholesterol but only 2 dogs survived the procedure after the second week. The intermittent injections probably did not supply an adequate level of nicotine in the blood for a sufficiently prolonged period to produce

Table I. Levels of serum cholesterol (mg./100 ml.) in dogs receiving daily nicotine

Dog number	No nicotine (Control)	Nicotine bitartrate (0.5 mg./Kg.)				Nicotine bitartrate (1.0 mg./Kg.)		No nicotine	
		Weeks							
		1	2	3	4	5	6		8
1	116	131	157	133	2 4	220	709	219	191
2	92	93	94	93	141	136	146	122	108
3	122	117	136	168	196	202	206	22/	197
4	155	230	273	246	239	241	220	228	190
5	172	199	1/6	163	181	176	178	164	159
6	139	199	210	232	230	208	160	180	183
7	193	275	728	238	40	224	231	187	205
8	190	283	247	253	303	234	260	259	241
9	120	122	164	187	186	169	189	156	151
Mean	144	185	187†	190†	216‡	201‡	200‡	194†	181†
± S.E.	±11.8	±23.1	±16.6	±18.5	±15.3	±11.4	±11.8	±14.4	±13.2

Mean of 6 daily determinations.
†p value of means relative to control < 0.05.
‡p value of means relative to control < 0.01.

Table II. Levels of serum cholesterol (mg./100 ml.) in control dogs not receiving nicotine

Dog number	Weeks								
	0	1	2	3	4	5	6	7	8
Received no injections									
10	120	—	115	119	116	101	113	97	98
11	160	151	147	158	150	160	163	153	148
12	137	137	129	147	131	147	133	138	129
13	145	16	—	152	—	148	151	—	140
14	173	184	—	177	—	181	—	167	178
15	1 3	1 2	—	170	110	128	137	—	117
Received injections of vehicle only									
16	178	170	177	164	164				
17	124	121	122	125	112				
18	183	187	177	176	168				
19	168	187	176	168	178				
20	183	173	190	185	197				

2.0 per cent glycerol and 2.0 per cent gelatin in water.

Table III *Mean levels of serum triglycerides (mg./100 ml. ± S.E.) in dogs receiving daily nicotine*

No nicotine (Control)	Nicotine bitartrate (0.5 mg./Kg.)				Nicotine bitartrate (1.0 mg./Kg.)		No nicotine	
	Weeks							
	1	2	3	4	5	6	7	8
42 ±5.1	44 ±4.3	46 ±4.3	46 ±5.7	45 ±4.6	42 ±4.9	42 ±3.6	44 ±4.0	41 ±3.8

Mean of 6 daily determinations.

a cholesterol effect, whereas the 4 hour infusions did. The use of the slow absorption vehicle permitted prolonged administration of nicotine and was also well tolerated by the animals. Secondly, the use of the slow absorption vehicle more closely simulated continuous human cigarette smoking; the dose of nicotine given daily approximated the amount absorbed by a human subject smoking 20 cigarettes daily.

The mechanism of the rise in cholesterol after nicotine has not been determined. It may be postulated, however, that the free fatty acids released from the depots increase liver free fatty acids, which may be a stimulus for the production of cholesterol. The absence of nicotine effect on the levels of serum triglycerides in these experiments cannot be explained; other investigators have also noted this after epinephrine.[1, 11]

No electrocardiographic or pathologic evidence of myocardial degeneration or atherosclerosis was detected in our dogs. In rabbits, Wenzel and associates[14] found no increase in aortic atherosclerotic lesions when nicotine was added to a hypercholesteremic diet and no areas of cardiac necrosis. However, Czochra-Lysanowicz and associates[15] found that nicotine increased the degree of aortic atherosclerosis. Dogs as a species are notably resistant to the development of atherosclerosis. In our experiments nicotine was given for 6 weeks, and hypercholesteremia was maintained during this period. Whether changes in the blood vessels or myocardium occur after a longer period of nicotine-induced hypercholesteremia should be investigated.

The hypercholesteremic effect of nicotine in dogs suggests the possibility of a similar effect of smoking in human beings. Carefully controlled long-term studies through the start and cessation of smoking are necessary in order to determine whether the statistical association of smoking and elevated blood cholesterol reflects a cause-and-effect relationship.

Summary

Dogs were given daily intramuscular injections of nicotine for a 6 week period and the effect on serum lipids was observed. The mean serum cholesterol level rose from 144 ± 11.8 mg. per cent to 216 ± 15.3 mg. per cent (50 per cent). The elevation of cholesterol was maintained until the administration of nicotine was stopped. It is suggested that this effect may be secondary to a nicotine-induced rise in free fatty acids.

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Changes in amino acid composition of aortic elastin with aging and atherosclerosis

*Martin Fitz-Patrick, M.D.**
Verne D. Hospelhorn, Ph.D.
Saranac Lake, N.Y.

Recent studies of the chemical composition of various components of the arterial wall have been reported to show changes with aging. Among others, these include a reduction in the content of acid mucopolysaccharides of the ground substance and differences in the amino acid composition of elastins isolated from the tunica media of aortas from young and old subjects.[1,2] It has been further proposed that a correlation exists between the content of acidic amino acids found in elastins of different ages and the degree of calcification noted in the media of older aortas.[4] Elastins isolated by alkaline extraction from pulmonary connective tissue of subjects of different ages have shown differences in their amino acid composition.[5] This communication reports on further differences in the amino acid composition of aortic elastins as related to age and to the degree of atherosclerosis.

Materials and methods

Portions of mid-thoracic aorta were obtained at the time of autopsy and stored in a freezer at -20 C. The ages of the subjects studied ranged from 6 months to 79 years. When thawed, the adventitia was stripped and discarded, and the remaining intima and media were minced, blended with water, and then treated by methods devised for the isolation of pulmonary connective tissue.[5,6]

Elastin was then isolated from powdered aortic connective tissue by alkaline digestion with 0.1N NaOH at 100°C for 45 minutes, hydrolyzed, and analyzed by a Beckman Spinco Model 120B amino acid analyzer using the buffer systems of Spackman, Stein, and Moore.[7] Duplicate analyses agreed within $\pm$ 3 per cent. The degree of gross atherosclerosis was recorded on inspection prior to cutting the aorta as follows: + intimal fatty flecks or streaks; ++ small subintimal lipid plaques; +++ necrosis of atheromatous plaques; ++++ ulceration and calcification of atheromatous plaques.

Results

Table I lists the amino acid residues found in aortic elastins of 13 subjects who ranged in age from 6 months to 79 years. Data record the amino acid nitrogen as per cent of the total nitrogen of each hydrolysate. The weight of dried elastin recovered from aortic connective tissue is expressed as per cent weight of original crude connective tissue (CCT). The degree of gross atherosclerosis on inspection is recorded. Most of the older subjects died

From the O'Do[illegible] Memorial Research Laborat[illegible] Will Rogers Hosp[illegible] Saranac Lake, N.Y., [illegible] the Dep[illegible] of Medicine, New York University School of Medicine, New York, N.Y.
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*Address: O'Donnell Memorial Research Laboratories, Will Rogers Hospital, Saranac Lake, N.Y. [illegible]

*Table I Amino acid composition of aortic elastins**

Amino acid	W R 17	W R 18	AH 1	AH 7	AH 16	AH 3
Age (yr)	½	1½	15	35	45	55
Hydroxyproline	1 00	1 20	90	71	90	88
Aspartic acid	29	19	12	39	54	44
Threonine	67	87	71	79	92	70
Serine	67	71	70	71	67	70
Glutamic acid	1 48	1 60	1 56	1 69	1 96	1 76
Proline	11 10	11 90	12 59	11 10	10 95	11 90
Glycine	29 30	33 00	30 48	29 60	30 20	27 70
Alanine	22 10	24 70	23 75	22 45	23 30	21 30
Valine	11 85	13 45	12 30	12 70	12 80	12 90
Methionine						09
Isoleucine	2 14	2 43	2 13	2 28	2 34	2 03
Leucine	5 18	5 93	5 04	5 58	5 62	5 65
Tyrosine	1 43	1 80	1 94	2 01	2 04	1 94
Phenylalanine	1 93	2 23	2 33	2 13	2 17	2 03
Lysine	1 24	1 55	77	86	1 00	1 06
Histidine				24	5	35
Ammonia	2 28	1 99	1 56	2 24	2 58	2 82
Arginine	1 91	2 04	1 92	2 36	2 67	2 91
Per cent recovery	95	100	98	98	100	97
Per cent of CCT	40	48	47	34	34	32
Atherosclerosis	0	0	0	+	++	++

*Values expressed as amino acid nitrogen per cent of total nitrogen.
CCT Crude connective tissue

as a result of atherosclerosis but the 7 individuals under 60 years of age died from unrelated diseases

Significant differences in the amino acid content of these adult elastins were noted but no consistent pattern of change was evident to us Lower values for aspartic acid glutamic acid arginine and histidine were observed in the younger aortic elastins as had been found in elastins isolated from pulmonary connective tissue of younger subjects by this same technique[3] No consistent change in the amino acid composition of aortic elastins was noted with relation to either the severity or duration of atherosclerosis

Discussion

In an earlier report Lansing and co-workers[5] found a lower content of glutamic acid and aspartic acid in aortic elastin isolated by this technique from a 15 year old subject that in elastin from older individuals Our studies further indicate that both aortic and pulmonary elastins isolated from even younger subjects contain lower amounts of these two amino acids and of arginine and histidine as well when compared to tissues from older individuals It is thought that these changes most likely reflect a differing vulnerability of young elastin to partial degradation under vigorous extraction techniques employing heat and alkaline conditions

There is increasing evidence that in vivo elastic tissue (as contrasted with elastin) is a protein complex which also contains carbohydrate and possibly lipid and that a portion of this complex is lost under vigorous conditions of isolation[10,11] Therefore we are at present using a less drastic technique with bacterial collagenase

AH-4	AH 9	AH 13	AH 18	AH 20	AH 19	AH 2
58	61	63	67	7?	72	79
80	1 02	1 02	1 04	1 09	97	97
40	67	87	73	70	79	56
45	76	96	1 04	74	92	90
40	71	1 01	83	9	79	67
1 74	2 05	2 31	2 19	1 80	2 24	1 91
11 50	11 25	11 15	11 25	13 95	10 65	11 70
28 10	28 00	29 40	29 90	30 25	26 0	26 55
23 50	21 30	21 80	22 90	23 35	20 40	20 00
12 30	14 60	17 00	13 10	12 65	12 10	12 00
13						
1 96	2 28	2 36	2 39	2 41	2 24	2 58
5 58	5 48	5 57	5 72	5 78	5 40	5 28
2 01	2 01	2 16	2 19	2 24	1 84	2 02
2 01	2 10	2 21	2 19	2 32	1 97	1 91
1 25	1 07	1 34	1 15	1 14	1 18	1 12
13	40	58	42	39	66	45
2 23	2 41	2 45	2 71	2 11	3 16	2 58
1 43	2 68	2 89	3 02	2 98	2 89	3 04
96	97	100	100	99	95	94
26	39	26	30	38	27	18
+++	++++	+++	+++	++++	++++	++++

from *Clostridium histolyticum* for isolating aortic elastin in order to study chemical changes associated with aging and atherosclerosis

Summary

Elastins have been isolated by hot alkaline extraction from the aortic connective tissue of subjects of different ages and their amino acid composition has been studied A lower content of aspartic acid glutamic acid and histidine was observed in the elastins from the aortas of younger subjects than in those from the aortas of older subjects Similar changes have been reported in elastins isolated by this technique from the lungs of young subjects No significant changes in amino acid composition of aortic elastins appeared to be associated with either the severity or duration of atherosclerosis when isolated by the technique of alkaline extraction

We wish to thank M and Mrs Gabino Lopez and Mrs Derrick May for valuable technical assistance

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Effect of 50 per cent sodium diatrizoate (Hypaque) on blood flow in the internal carotid artery of man

*George T Tindall M D**
Joseph C Greenfield Jr M D
William Dillingham B A
J Fletcher Lee M D
Durham N C

Considerable investigative work has been done in an effort to define the changes in circulatory dynamics which follow the intravascular administration of contrast media. Alterations in blood pressure, heart rate, and cerebral blood flow have been studied in various experimental animals.[1-11] Also, changes have been noted in both the blood pressure and the pulse rate in man during cerebral angiography.[12-14] However, the response of the cerebral vessels to the intracarotid administration of contrast media is debated: some workers believe that vasospasm occurs,[4,7,15] whereas others believe that vasodilatation is the principal change.[8,9,11,17] To our knowledge, no quantitative measurements of either partial or total cerebral blood flow have been obtained after the injection of contrast media into the internal carotid artery of man. Therefore, a study of simultaneously determined flow and pressure in the internal carotid artery of man after the intracarotid administration of 50 per cent sodium diatrizoate (Hypaque†), a contrast agent currently in use in many clinics for cerebral angiography, should clarify this question.

Method and case material

These studies were made in 10 male patients who were undergoing surgery on the carotid vessels in the neck so that a cancer-chemotherapy drug‡ could be infused directly into the internal carotid artery. Craniotomy and subtotal resection of a brain tumor had been performed from 10 to 14 days prior to the dissection in the neck in each subject. In 6 cases the tumor type was a glioblastoma multiforme (Patients 1, 2, 5-8, Table I), in 3 patients an astrocytoma (Patients 3, 4, and 10, Table I), and in 1 patient an oligodendroglioma (Patient 9, Table I).

The surgical procedure on the neck was done using general anesthesia consisting of a mixture of halothane (0.5 per cent), nitrous oxide (49.5 per cent), and oxygen (50 per cent). The common carotid and proximal portions of the external and internal carotid arteries were dissected free from surrounding tissue. A polyvinyl catheter (No. VX 044) was inserted into the superior thyroid artery and threaded down the vessel so that the tip of the catheter was just within the carotid bifurcation. The remaining branches of the

From the Division of Neurosurgery [illegible] Department of [illegible] Duke [illegible] Medical Center [illegible] Veterans Administration Hospital, Durham, N. C.
Received for publication April 13, 1964
*Address: Veterans Administration Hospital [illegible] Durham, N. C.
†Made [illegible] by Winthrop Laboratories, New York, N. Y.
‡[illegible]

ipsilateral external carotid artery were then ligated The hinged probe of a Kolin Kado type of electromagnetic flowmeter (EMF) was placed about the common carotid artery approximately 4 cm proximal to the bifurcation[13] A Crutchfield clamp* was also placed about this vessel distal to the EMF probe The stem of the Crutchfield clamp polyvinyl catheter and insulated leads to the EMF probe were brought out through the edges of the wound which was closed in anatomic layers with silk sutures Measurements of flow and pressure in the internal carotid artery were obtained in the awake state in 9 patients 2 to 8 hours after the general anesthesia had been discontinued The patients received no other medication prior to this procedure and were studied while they were in the supine position After the satisfactory recording of control flow and pressure a rapid injection of 50 per cent sodium diatrizoate (3 to 10 c c in each patient Table I) was given into the internal carotid artery through the polyvinyl catheter Recordings of both flow and pressure were obtained continuously for 60 seconds after this injection In one patient (Patient 3 Table I) these measurements were made while the patient was still under general anesthesia

Blood flow was measured with a Kolin Kado type EMF[1] The zero flow reference was obtained by temporarily occluding the artery with the Crutchfield clamp The EMF was calibrated after the procedure by passing known quantities of physiologic saline through the probes in a given period of time The calibration factor for the probes i e flow per unit EMF signal remained within a S D of ±5 4 per cent during the period of this study Arterial pressure was measured with a Statham P23Db strain gauge connected to the polyvinyl catheter Mean values of both pressure and flow were obtained by electrical integration

In order to assess the physiologic state of the patients prior to the intracarotid administration of 50 per cent sodium diatrizoate samples of blood were drawn from the brachial artery for measurement of pCO and pO These determinations were done with an Instrumentation Laboratories meter Model 113 The lumbar subarachnoid space was entered with an 18 gauge lumbar puncture needle from 30 to 60 minutes after the intracarotid administration of 50 per cent sodium diatrizoate The cerebrospinal fluid pressure was measured at this time with a Statham P23Db transducer connected directly to the needle All recording of data was carried out on a Sanborn Model 850 eight channel direct writing oscillograph

After the studies had been completed the cancer chemotherapy drug was infused through the polyvinyl catheter and the patients were then returned to the operating room for removal of the Crutchfield clamp EMF probe and the catheter

Standard statistical methods were used in analyzing data The peripheral vascular resistance (p v r) of the region supplied by the internal carotid artery was calculated as

$$\text{p v r} = \frac{\text{Mean blood pressure mm Hg}}{\text{Mean blood flow c c min}}$$

Results

Although the blood pressure and flow were measured continuously only values obtained during the control state and at 5 10 20 30 and 60 seconds after completion of the injection of 50 per cent sodium diatrizoate were analyzed These data are summarized in Table I and illustrated in Fig 1

The average control heart rate was 105 beats per minute In 2 subjects (Patients 1 and 2 Table I) a period of asystole that lasted for 2 and 3 seconds respectively occurred shortly after the injection Thus the 5 second data on these subjects were not included The heart rate decreased at 5 and 10 seconds to a mean value of 96 and 88 beats per minute respectively These differences are significant ($p < .05$) from the control values The heart rate returned to control levels at 20 seconds and remained constant

There was an increase in the flow of blood in the internal carotid artery after the injection of 50 per cent sodium diatrizoate in every case The average value for control blood flow was 160 c c per

*The Crutchfield clamp [illegible]

minute (S D ±43) The average flow for the group increased at 5 (178 c c per minute) and 10 seconds (217 c c per minute) reaching its greatest average value at 20 seconds (242 c c per minute S D ±89) The difference from control flow at 20 seconds is significant ($p < .01$) The average value for flow at 30 and 60 seconds was 221 and 193 c c per minute respectively

The average control value for mean arterial pressure was 103 mm Hg (S D ±20) Although the pressure rose slightly at 10 and 20 seconds the increase was not significant ($p > .05$)

The average value for control p v r was 0 69 (S D ±0 24) The p v r decreased significantly ($p < .05$) at both 5 seconds [0 61 (S D ±0 19)] and at 10 seconds [0 59 (S D ±0 24)] At 20 seconds the p v r fell significantly ($p < .01$) to 0 49 (S D ±0 18) its lowest value At 30 and 60 seconds the p v r was 0 51 (S D ±0 14) and 0 57 (S D ±0 16) respectively

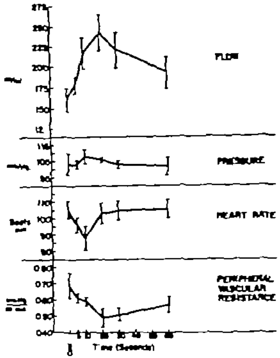


Fig 1 Average values for blood flow blood pressure heart rate and peripheral vascular resistance during the control state and after the injection of 50 per cent diatrizoate in 10 subjects The small cross vertical bar represent the ± standard errors

Discussion

The control values for flow in a single internal carotid artery in these 10 patients ranged from 111 to 220 c c per minute with an average for the group of 160 c c per minute These values are less than might be expected for normal subjects However these studies were carried out in a group of patients in whom craniotomy and partial resection of a brain tumor had been performed from 10 to 14 days prior to the study The fact that the major part of the tumor and some normal brain tissue supplied by this internal carotid artery had been removed probably contributed to the seemingly low flow Other factors were the slightly reduced values for pCO_2 and the elevated pressure of the cerebrospinal fluid

The vascular responses which follow the injection of various contrast media into the carotid artery in experimental animals have been studied extensively by other investigators Ahgstrom Lindgren and Tornell[9,10] obtained an increase in cerebral blood flow in dogs and cats after the injection of contrast media into the internal carotid artery The increase in blood flow after the injection of sodium diatrizoate never exceeded 100 per cent and the duration of the effect lasted approximately 2 minutes The results of the present study in man are consistent with these findings The increase in blood flow in the internal carotid artery after the intracarotid injection of 50 per cent diatrizoate shown in this study would imply that the mechanism of the occasional adverse clinical reaction to arteriography is not due to a decrease in blood flow but rather to some other cause

A transient decrease in blood pressure and heart rate after injection of contrast media into the circulatory system has been noted previously in man and experimental animals In cats Lindgren and Tornell reported a decrease in blood pressure and heart rate after the injection of sodium acetrizoate into the carotid artery In carotid angiography with sodium acetrizoate Critz[11] observed changes in blood pressure and heart rate in most of his patients The changes usually consisted of a decrease in blood pressure of short duration with an associated bradycardia and arrhythmia Fischer Eckstein and

Perrett[1] noted a decrease in blood pressure and bradycardia in patients who were undergoing cerebral angiography with 60 per cent Renografin (methylglucamine salt of the diatrizoate compound) and 50 per cent sodium diatrizoate In general these responses were minor and brief On the other hand Smolik and Nash[13] found no significant changes in blood pressure or heart rate in patients during carotid angiography carried out with 50 per cent sodium diatrizoate In the present study a significant decrease in heart rate that lasted for approximately 20 seconds occurred after the intracarotid injection of 50 per cent sodium diatrizoate There were no significant or consistent changes in arterial pressure

An increase in the flow of blood to the brain after the administration of contrast media into its vascular bed is not a finding restricted to this organ Increased flow to other organs after the administration of contrast agents has been reported by several investigators Sako[19] noted an increase in femoral arterial flow in both dogs and man after the injection of contrast media included among which were sodium acetrizoate iodopyracet and sodium diatrizoate He believed that the increased flow resulted from a lowering of vascular resistance through vasodilatation Lindgren and Tornell[1] observed vasodilatation and an increase in blood flow in the skeletal muscle and intestine of cats after the injection of sodium acetrizoate and sodium diatrizoate into the vascular bed of these tissues

Although some workers have reported vasospasm[4,7,16] most investigators have found that the principal vascular reaction to an infusion of contrast medium is transient vasodilatation In studies in cats Schmidt[8] observed vasodilatation in the pial arteries after the injection of contrast media into the carotid artery He did not observe vasospasm at any time even when high concentrations of the contrast media were used In pathologic studies Bloor Wrenn and Margolis[17] noted dilatation

Table I Effect of the intracarotid administration of 50 per cent sodium diatrizoate on mean blood flow and intravascular pressure in the internal carotid artery

Patient	Age (yr)	Amount injected (cc)	Arterial pCO (mm Hg)	Arterial pO (mm Hg)	Cerebrospinal fluid pressure (mm H₂O)	Control	Time after injection (sec) 5	10	20	30	60
1	4ɔ	8	32 3	59 0	—	F 111	—	13?	204	204	—
						P 106	—	106	111	111	104
?	39	10	37 0	78 5	—	F 207	—	423	467	449	311
						P 88	—	64	8[illegible]	102	90
3	41	3	24 0	200 0	—	F 137	145	150	17ɔ	175	163
						I 149	149	152	141	141	141
4	38	8	—	—	260	F 205	205	?55	238	238	230
						I 85	8?	90	90	87	87
5	49	3	35 8	81 0	—	F 135	144	148	172	197	172
						I 108	88	108	112	104	101
6	32	8	38 0	78 0	276	F 154	154	176	190	176	151
						I 88	88	96	96	84	88
7	ɔ	8	38 6	64 0	359	F 220	294	308	290	248	234
						P 128	140	160	128	120	120
8	[illegible]	8	38 0	69 0	195	F 113	161	161	178	158	133
						I 96	104	108	96	98	96
9	50	8	32 8	81 5	250	F 198	186	250	281	229	?13
						I 92	88	112	9?	92	96
10	3(	8	36 8	75 0	358	F 117	135	165	225	133	128
						I 88	85	88	100	90	90

[illegible]
F Flow in cubic centimeters per minute P Pressure (in millimeters of mercury)

of the parenchymal vessels of all caliber as an early change after cerebral angiography Although the response of localized areas of the cerebral vasculature may vary the findings of our study imply that the over all response of the cerebral blood vessels to the injection of contrast media is one of immediate vasodilatation Since the p v r decreased immediately after the injection and remained depressed through out the observation period no evidence for generalized vasospasm was found

Summary

1 The effect of the intracarotid injec tion of 50 per cent sodium diatrizoate on flow in the internal carotid artery intra vascular pressure in the carotid artery and heart rate has been determined in 10 patients

2 The average control value of mean flow in these subjects was 160 c c per minute After the injection of 50 per cent sodium diatrizoate there was an immediate increase in flow in the internal carotid artery which reached an average peak at 20 seconds of 242 c c per minute for the group and which lasted throughout the ob servation period of 60 seconds

3 There were no consistent or sig nificant changes in arterial pressure

4 The heart rate decreased significantly immediately after injection but returned to normal in 20 seconds

5 There was a significant decrease in peripheral resistance in the vascular bed of the injected internal carotid artery which began within 5 seconds and which persisted throughout the observation period of 60 seconds

6 These data show that the over all vascular response after an intracarotid injection of 50 per cent sodium diatrizoate is that of vasodilatation

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Effect of l-norepinephrine on right atrial pressure and the "square wave response" to the Valsalva maneuver

A. O'Neill, M.D.
*L. Cudkowicz, M.D.**
Halifax, Canada

An abnormally sustained systolic and diastolic arterial blood pressure during continuous airway straining, and the total absence of bradycardia and "overshoot" in systemic arterial pressure during Phase 4 of the Valsalva maneuver constitutes the essential characteristics of the so-called "square wave phenomenon." This phenomenon was first described by Hamilton and others[1] and was subsequently attributed to heart failure.[2-4] However, Gorlin and associates[5] observed this response in patients with constrictive pericarditis and McIlroy[6] noted it in one patient with an atrial septal defect who was not in congestive heart failure. Recently, 4 patients with atrial septal defects and 3 with constrictive pericarditis were briefly reported on[7] because of typical "square wave responses" in the absence of congestive heart failure. The mean resting right atrial pressure in these 7 patients was 16.5/11.5 mm. Hg. The assumption was made that the common denominator in patients who exhibited the "square wave phenomenon" was probably a critically elevated central venous and right atrial pressure and that this response might be induced in normal individuals by an elevation of the central venous and right atrial pressures through the action of a continuous infusion of l-norepinephrine. This specific effect of l-norepinephrine in normal man has been well documented[8,9] since the original observation by Fowler and associates.[9]

In the present study, the effect of an infusion of l-norepinephrine upon right atrial pressure before and after the Valsalva maneuver will be compared with the right atrial pressures in the resting state and with the pressures that obtained in patients showing the "square wave response" as a result of a variety of heart disease.

Material

This study comprises 22 patients who suffered from a variety of cardiopulmonary diseases and required routine catheterization of the right side of the heart. Thirteen of these patients showed the square wave response although only 6 of these were in congestive heart failure. Four patients in this group, not in failure, suffered from atrial septal defects and 3 from constrictive pericarditis. The other 9 patients exhibited a normal response

From th[illegible] Department of Medicine, Dal[illegible] University and the Victoria Ge[illegible] Hospital, Halifax, N[illegible] Scotia, Canada.

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*Address: Department of Medicine, D[illegible] University, Halifax, Nova Scotia, Canada.

Table I Material

Patient	*Diagnosis*	*Response to Valsalva maneuver*
Group I		
1	Mitral stenosis	Normal
2	Mitral stenosis	Normal
3	Atrial fibrillation (idiopathic)	Normal
4	Mitral incompetence	Normal
5	Cor pulmonale	Normal
6	Mitral incompetence	Normal
7	Mitral stenosis	Normal
8	Bronchial asthma	Normal
9	Emphysema	Normal
Group II		
10	Mitral stenosis and incompetence (in congestive failure)	Square wave
11	Aortic incompetence (in congestive failure)	Square wave
12	Mitral stenosis (in congestive failure)	Square wave
13	Mitral incompetence (in congestive failure)	Square wave
14	Cor pulmonale (in congestive failure)	Square wave
15	Cor pulmonale (in congestive failure)	Square wave
16	Atrial septal defect	Square wave
17	Atrial septal defect	Square wave
18	Atrial septal defect	Square wave
19	Atrial septal defect	Square wave
20	Constrictive pericarditis	Square wave
21	Constrictive pericarditis	Square wave
22	Constrictive pericarditis	Square wave

of the peripheral arterial blood pressure to the Valsalva test. Two of these patients had large left atria due to predominant mitral incompetence, 6 suffered from a variety of heart diseases and 1 patient from long-standing bronchial asthma (Table I).

Methods

Airway strain during the Valsalva maneuver was maintained by forced expiration from the mid-inspiratory position against a mercury manometer at a pressure of about 40 mm. Hg and lasted for approximately 15 seconds. Intra-arterial pressure tracings were obtained through a 17 gauge Cournand needle introduced under local anesthesia into a femoral or brachial artery. Right atrial pressures were recorded during cardiac catheterization. Both needle and catheter were kept patent by a continuous infusion of heparinized saline. The zero level used was 10 cm. from the top of the table.[19] Simultaneous pressure records from the artery and right atrium via two Sanborn transducers were continuously inscribed on a direct writing recorder. The right atrial and central venous pressures were not corrected for the increments of intrathoracic pressure during airway straining. The patients were asked to carry out the Valsalva maneuver after appropriate intervals. After the basal studies had been completed, the subjects of Group I who had the normal response received an infusion through the catheter into the right atrium of 4 micrograms of l-norepinephrine in normal saline. During the period of infusion, which lasted for a minimum of 10 minutes, the Valsalva maneuver was repeated on several occasions.

Results

Group I. Normal response. Patients 1 to 9 were used as controls because of the normal response of their peripheral blood pressure to the Valsalva maneuver.

Table II compares the resting right atrial pressure with that during Phase 4 of the Valsalva maneuver. Elevation in mean right atrial pressure from 6.7/2

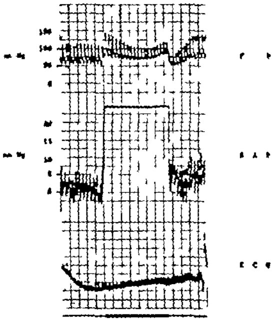


Fig 1 Mitral teno Norm l r ponse to the Valsalva maneuver F A P Femor l arteri l pres su e R A P Right trial pre ure rise during over hoot I per peed of 2 5 mm per se ond Mouth pre ure f 40 mm Hg The period of strain is represented by the broad b r on the time line

to 12 2 7 6 mm Hg was found at the time of the overshoot of the peripheral arterial blood pressure The difference in right atrial pressure between the resting and Phase 4 levels is statistically significant (p = < 0 01) A typical tracing showing simultaneously the normal arterial blood pressure and the responses of right atrial pressure to the Valsalva maneuver is seen in Fig 1

Group II Square wave response This group consisting of Patients 10 to 22 showed a square wave response to the Valsalva maneuver In contrast to Group I no rise in right atrial pressure occurred during Phase 4 (Table III) The mean right atrial systolic pressures before and after the Valsalva test were 16 5 mm Hg and the mean diastolic pressures were 11 6 mm Hg respectively Statistically no significant difference between these pressures could be established (p = > 0 1) Group II also differs from Group I in that in the former group the mean resting right atrial pressure was 16 5/11 6 mm Hg whereas in the latter group it was 6 7/2 7 mm Hg (Table IV) These differences are again statistically significant (p = < 0 01) Fig 2 illustrates the peripheral arterial square wave response to the Valsalva maneuver with a simultaneously recorded tracing from the right atrium before and after release of exhalation against resistance

Group I after infusion of l norepinephrine (square wave response) The 9 patients of Group I received an intravenous infusion of l norepinephrine which was continued for a period of 10 minutes before measurements of right atrial pressure were taken After this time the maximum effect of l norepinephrine upon right atrial pressure was usually apparent In our experience the square wave phenomenon did not always emerge at the time of a maximum vasoconstrictor effect upon the peripheral arterial circulation and often as much as 20 minutes of infusion were necessary before an unequivocal square wave appeared in the peripheral arterial pulse pressure record

Intravenous infusion of l norepinephrine causes a significant elevation of resting right atrial pressures from a mean of 6 7 2 2 to a mean of 15 8/10 3 mm Hg

Table II Comparison of resting and Phase 4 right atrial pressures with a normal peripheral arterial blood pressure response to the Valsalva maneuver (Group I)

Patient	Systolic right atrial pressure (mm Hg)		Diastolic right atrial pressure (mm Hg)	
	Resting	Phase 4	Resting	Phase 4
1	8	11	3	5
2	6	10	4	8
3	6	11	4	6
4	7	12	2	9
5	4	13	0	10
6	7	12	3 5	8
7	5	12 5	0	3 5
8	5	11	0	4
9	12	17	8 5	15
Mean	6 7	12 2	2 7	7 6
S D ±	2 3	2 0	2 7	3 5
Significance of difference	p = < 0 01		p = < 0 01	

Table III Resting and Phase 4 right atrial pressures in patients who showed the square wave phenomenon to the Valsalva maneuver

Patient	Systolic right atrial pressure (mm Hg)		Diastolic right atrial pressure (mm Hg)	
	Resting	Phase 4	Resting	Phase 4
10	17	17	12	12
11	15	15	10	10
12	16	16	10	10
13	23	23	19	19
14	15	15	9	9
15	16	16	12	12
Mean	17.0	17.0	13.7	13.7
S D ±	3.1	3.1	4.2	4.2
16	13	13	10	10
17	12	12	9	9
18	11	11	8	8
19	16	16	13	13
Mean	13.0	13.0	10.0	10.0
S D ±	2.2	[illegible]	2	2.2
20	20	20	12	12
21	21	21	14	14
22	19	19	13	13
Mean	20.0	20.0	13.0	13.0
S D ±	1.0	1.0	1.0	1.0
Total of 13				
Mean	16.5	16.5	11.6	11.6
S D ±	3.5	3.5	9	2.9
Significance of difference	$p = > 0.1$		$p = > 0.1$	

($p = < 0.01$) (Table V) Thus l norepinephrine raises the resting right atrial pressure to a level similar to that seen in patients who show a square wave response as a result of disease and there is no significant difference ($p = > 0.1$) in the mean right atrial pressures of the groups showing the square wave response (see Table VI and Fig 3) Table VII shows that the elevation in resting right atrial pressure after a 10 minute infusion of l norepinephrine persists at that level during Phase 4 and that there is no significant difference between them ($p = < 0.1$)

The behavior of the pulmonary arterial pressure is precisely the same as that of the right atrial pressure and overshoots during Phase 4 of the Valsalva maneuver in normal patients (Fig 4) whereas it remains unchanged in the patients of Group II and in patients given infusions of l norepinephrine (Fig 5) Similar patterns apply to the pulmonary capillary wedge pressure (Fig 6)

Discussion

Table I shows that 6 patients of Group II suffered from congestive heart failure and responded with the square wave phe

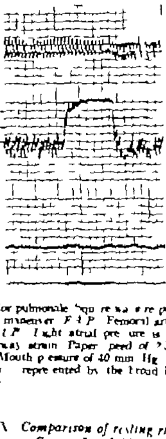


Fig 2 Cor pulmonale Square wave response to the Valsalva maneuver *F A P* Femoral arterial pressure *R A P* Right atrial pressure is unchanged after airway strain Paper speed of 25 mm per second Mouth pressure of 40 mm Hg The period of strain represented by the broad bar on the time line

Table IV Comparison of resting right atrial pressures in Groups I and II

	Resting right atrial pressures (mm Hg)	
	Systolic	Diastolic
Group I (N = 9) Mean ± S D	6.7 ± 2.3	2.7 ± 7
Group II (N = 13) Mean ± S D	16.5 ± 3.5	11.6 ± 2.9
Significance of difference	$p = < 0.01$	$p = < 0.01$

nomenon to the Valsalva maneuver. The mean right atrial pressure before the Valsalva maneuver in this group was 17.13.7 mm. Hg, and it remained at that level during Phase 4 after the maneuver (Table III). Similarly, the 4 patients with atrial septal defects who responded in an identical manner, but who were free from heart failure, also maintained their resting mean right atrial pressure (13/10 mm. Hg) during Phase 4. In the 3 patients with constrictive pericarditis and without heart failure, the mean resting right atrial pressure was higher than in patients with atrial septal defects, namely, 20.0/13.0

Table V. Resting right atrial pressures before and after infusion of l-norepinephrine

Patient	Resting systolic right atrial pressure (mm. Hg)		Resting diastolic right atrial pressure (mm. Hg)	
	Before	*After*	*Before*	*After*
1	8	15	3	10
2	6	14	4	17
3	6	16	4	10
4	7	18	2	12
5	4	16	0	11
6	[illegible]	20	3.5	17
7	5	11.5	0	2.5
8	5	17	0	5
9	1	15	8.5	15
Mean	6.7	15.8	2.7	10.3
S.D. ±	2.3	2.4	2.7	4.3
Significance of difference	$p = < 0.01$		$p = < 0.01$	

Table VI. Resting right atrial pressure in Group II and Group I after infusion of l-norepinephrine

	Resting right atrial pressures	
	Systolic (mm. Hg)	*Diastolic (mm. Hg)*
Group II (N = 13) Mean ± S.D.	16.5 ± 3.5	11.6 ± 2.9
Group I after l-norepinephrine (N = 9) Mean ± S.D.	15.8 ± 2.4	10.3 ± 4.2
Significance of difference	$p = > 0.1$	$p = > 0.1$

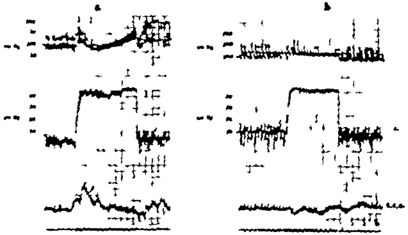


Fig. 3. Bronchial asthma. Comparison of femoral arterial and right atrial pressure responses to the Valsalva maneuver before (*a*) and after (*b*) infusion of l-norepinephrine. *a*, Normal femoral arterial pressure response (*F.A.P.*) and normal elevation in right atrial pressure at time of overshoot (*R.A.P.*). *b*, Square wave response of femoral arterial pressure (*F.A.P.*) and resting right atrial pressure (*R.A.P.*) elevated and unchanged after [illegible] strain. Paper speed of 2.5 mm. per second. Mouth pressure of 40 mm. Hg. The period of strain is represented by the broad bar on the time line.

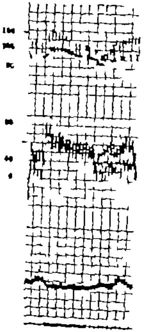


Fig 4 Mitral stenosis Normal re ponses to the Valsalva maneuver F A P Femoral arterial pressure P A P Pulmonary arterial pressure Paper speed of 2 5 mm per second Mouth pressure of 40 mm Hg The period of strain is represented by the broad bar on the time line

were able to demonstrate a 22 per cent increase in cardiac output in women at the time of release of airway straining The effect of the Valsalva maneuver on the venous circulation is less clear but appears to be equally profound Bolt and associates[1] and Stucki[17] observed in normal patients a throttling of the superior vena cava and partial closure of the inferior vena cava during the height of Phase 2 In addition Stucki also stressed the re duction in the size of the heart and pul monary artery in the same phase in sub jects yielding the normal blood pressure response whereas in patients with the square wave response neither the reduction in the size of the heart nor a cutoff in venous return to the right atrium could be demonstrated Gorlin and associates[4] sug gested that the difference between the normal and abnormal responses to the Valsalva maneuver can best be explained in terms of the Starling curve of ventricular function This same contention would presumably also hold for the actual phase

mm Hg and remained unaltered after the Valsalva maneuver The maintenance of right atrial pressure at resting levels during Phase 4 is as distinct a feature as the square wave pattern of arterial blood pressure which distinguishes the patients of Group II Patients who responded normally to the Valsalva maneuver showed a clear cut rise in mean right atrial pres sure from 6 7 2 7 to 12 2/7 6 mm Hg during Phase 4

The Valsalva maneuver produces its main effects on systemic arterial blood pressure largely as a result of baroceptor responses in the arterial tree stemming from changes in left ventricular stroke volume The reflex effects are primarily reflected in the bradycardias of Phases 1 and 4 and in the vasoconstriction per sisting from Phase 2 through to the onset of the overshoot With the evolution of Phase 2 in the normal person the tachy cardia and fall in pulse pressure are as sociated with a decline in cardiac output[11] This is reversed during the development of Phase 4 and Booth and associates

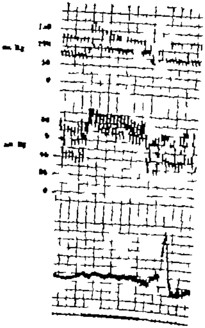


Fig 5 Mitral stenosis Responses to the Valsalva maneuver after the infusion of l norepinephrine F A P Femoral arterial pressure (square wave) P A P Pulmonary arterial pressure (square wave) Paper speed of 2.5 mm per second Mouth pressure of 40 mm Hg The period of strain is represented by the broad bar on the time line

Table VII Resting right atrial pressure and post Valsalva (Phase 4) right atrial pressure after infusion of l norepinephrine (Group I)

Patient	Systolic right atrial pressure (mm Hg)		Diastolic right atrial pressure (mm Hg)	
	Resting	Phase 4	Resting	Phase 4
1	15	15	10	10
2	14	14	12	12
3	16	16	10	10
4	18	18	12	12
5	16	16	11	11
6	20	20	17	17
	11 5	11	7 5	0
8	17	16	5	6
9	15	15	13	13
Mean	15 8	15 7	10 3	10 1
S D ±	2 4	2 5	4 3	4 8
Significance of difference	p = > 0 1		p = > 0 1	

differences during the Valsalva maneuver which clearly indicates significant changes in right and left atrial pressures in the normal patients at least during the evolution of the overshoot

The patients of Group II in this series who showed the square wave phenomenon had a mean right atrial pressure at rest of 16 3 11 0 mm Hg which is in contrast to the 6 7 2 7 mm Hg found in the normal Group I At this level of central venous and right atrial pressure the airways strain pressure of 40 mm Hg fails to impede venous return and ventricular stroke volume is insufficiently reduced to bring the baroceptor reflexes into play Proof for this assumption awaits comparative measurements of stroke volume during Phase 2 of the Valsalva maneuver in normal patients and in those showing the square wave response

The ability to convert the normal response of arterial blood pressure to the Valsalva maneuver into the square wave phenomenon by means of infusion of l norepinephrine afforded an opportunity for a comparison of the levels of right atrial pressure in subjects free from heart failure The elevation of the mean resting right atrial pressure after l norepinephrine and its fixation at the elevated level during Phase 4 brings these previously normally responding subjects into the same range of right atrial pressure as that which obtained for the patients with heart failure in Group II Thus the square wave response in the presence of an increment in intrathoracic pressure not exceeding 40 mm Hg becomes solely indicative of an elevated mean central venous and right atrial pressure of approximately 13 mm Hg

l norepinephrine exerts an initial vasoconstrictive action on peripheral arterioles and through the aortic depressor baroceptors initiates a bradycardia in response to the rising blood pressure Duner and von Euler[14] during infusions of norepinephrine in cats noted falls in blood pressure to below the preinfusion level after and often during constant and prolonged infusion Similarly Lever and associates[18] demonstrated a similar decline in the initially raised arterial blood pressure after intravenous infusions of norepinephrine and suggested that vasodilatation

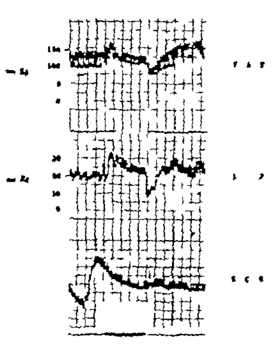


Fig 6 Mitral stenosis Normal response to the Valsalva maneuver F A P Femoral arterial pressure L A P Pulmonary wedge pressure showing significant rise during overshoot Paper speed 5 mm per second Mouth pressure 40 mm Hg The period of strain is represented by the broad line on the time line

gradually occurred in muscle and gut during the later stages of the infusions which was not prevented in muscle after denervation The same authors attributed this effect to a circulating vasodilator substance produced during intravenous infusion of l norepinephrine The slow evolution of the square wave response in the patients of Group I in the present study who received infusions of l norepinephrine has already been stressed *and often 10 or more minutes* were required before unequivocal patterns emerged A direct effect of l norepinephrine on venous tone was the explanation offered by Fowler and associates[9] for the elevation of right atrial pressure Alternatively the slow rise in mean right atrial filling pressure which accompanies the continuous infusion of l norepinephrine until full patency of the great veins persists even during increments in intrathoracic pressure of 40 mm Hg suggests an additional and more slowly developing effect upon the myocardium arising from powerful efferent vagal impulses which are also responsible for the bradycardia

Summary

Right atrial pressures were measured in 22 patients before and immediately after the cessation of airway straining In 9 patients (Group I) who showed a normal response of the peripheral arterial blood pressure to the Valsalva maneuver the resting mean right atrial pressure of 6 7 2 7 mm Hg rose to a mean of 12 2/7 6 mm Hg ($p = < 0.01$) during Phase 4 of the overshoot Thirteen patients in Group II including 6 with congestive heart failure responded with the square wave phenomenon to the Valsalva maneuver The resting mean right atrial pressure of 16 5/11 6 mm Hg remained unchanged after cessation of airway straining ($p = > 0.1$) and differed significantly from that of Group I ($p = < 0.01$)

Infusion of l norepinephrine (4 micrograms per minute) into the right atrium of the 9 patients of Group I led to the emergence of the square wave response to the Valsalva maneuver within approximately 10 minutes of the infusion and subsequent to the maximum elevation in peripheral arterial blood pressure The resting mean right atrial pressure rose significantly from 6 7/? to 15 8 10 3 mm Hg ($p = < 0.01$) and remained unchanged after the Valsalva maneuver i e 15 7/10 1 mm Hg ($p = > 0.1$) No statistical difference obtained between the resting mean right atrial pressures of patients who showed the square wave response (Group II) and those of the patients who received infusion of l norepinephrine ($p = > 0.1$) and it is suggested *that an elevated central venous and right atrial mean pressure of approximately* 13 mm Hg in the presence of an increment of intrathoracic pressure not exceeding 40 mm Hg becomes associated with the square wave phenomenon

We would like to thank Miss J Thomson for her able assistance and also Mr I Diamond Dalhousie University Medical Photography Department for the reproduction of the tracings

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Lymphangiography: An improved technique of lymphatic cannulation

*Rodney M. Patterson, M.D.**
C. Thorpe Ray, M.D.
Columbia, Mo.

During the past decade clinical lymphangiography has evolved from a technical challenge into a useful diagnostic procedure. It is currently being applied with increasing frequency in the evaluation of patients with disorders of the lymphatics and lymph nodes. More recently, treatment of malignancies involving the lymphatic system has been undertaken by infusing chemotherapeutic agents and radioisotopes directly into peripheral lymphatics.[1,2]

Kinmonth and associates are credited with the initiation of direct lymphangiography in human beings. The technique which they described,[*] with minor modifications,[...] is the one customarily employed for intralymphatic injections. The salient feature of the method is the introduction of a small-gauge needle into a peripheral lymphatic. We initially employed this method for intralymphatic injections in our patients, but subsequently we have adopted the use of polyethylene tubing for lymphatic cannulation, since earlier experience in animal studies[1] indicated that cannulae are superior to needles for this purpose.

We believe that this technique of lymphatic cannulation, because of its simplicity and economy, will lead to a more widespread use of lymphangiography as a diagnostic procedure. In addition, the technique described here eliminates certain of the difficulties which have been encountered by others in their early attempts at direct cancer chemotherapy of the lymphatic system.

Materials

Although all implements may be fashioned at the bedside at the time of lymphatic cannulation, we have found it convenient to prepare several "lymphogram sets" which are sterilized and ready for use at all times. Each set consists of a Petri dish containing the following items (Fig. 1): (A) several cannulae with tips of different diameters, (B) a stylette of proper length for all cannulae in the set, and (C) one syringe adapter and extension.

Repeated gas sterilization does not adversely effect any of the materials, and therefore a single lymphogram set may be used for multiple lymphatic cannulations.

The lymphatic cannulae are prepared by holding a piece of polyethylene tubing (P.E. 90) briefly above a flame and quickly drawing it out as far as possible. The tip is cut off squarely at the desired diameter. It is advantageous to prepare several cannulae with tips of different diameters in order to allow selection on the basis of the size of particular lymphatic at the time of cannulation. The cannulae are

From the Department of Medicine, University of Missouri School of Medicine, Columbia, Mo.
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*Present address: Department of Medicine, University of Missouri School of Medicine.

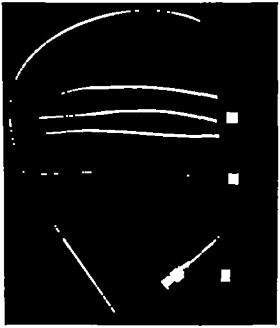


Fig 1 Lymphatic cannulation set See text for detail

shortened to fit the stylette by cutting off excess tubing

The stylette is devised by making a right angle bend in an ordinary 18 to 20 gauge needle stylette at approximately 2 mm from one end The stylette when inserted into its cannula should hook on the edge of the proximal end and not extend beyond the tapered tip of the cannula at the other end

The extension consists of a blunt 20 gauge needle with hub removed which is inserted into one end of a 10 to 15 inch length of polyethylene tubing (PE 90) The other end of the tubing is fitted to a syringe adapter

Method

The procedure is described in consider able detail because it is our impression that failure to give attention to these de tails is responsible for most unsuccessful attempts to cannulate lymphatics

Several peripheral lymphatics are usually visible through the intact skin shortly after a vital blue dye has been injected subcutaneously The lymphatic which has the longest and straightest course is se lected for cannulation and a large wheal (2 cm in diameter) is raised directly over it by the intradermal injection of a local anesthetic The large wheal not only anesthetizes the skin well but lessens the possibility of inadvertently cutting the lymphatic when the skin incision is made Furthermore it increases tissue pressure which aids in hemostasis and loosens the connective tissue to facilitate the subse quent dissection A skin incision made parallel to the long axis of the lymphatic exposes a longer segment of the duct than does a transverse incision of comparable size Furthermore it permits the lymphatic to be approached with the cannula entering the incision through its apex rather than more awkwardly over the skin edge of a transverse incision The skin edges are retracted by 3 0 silk sutures placed at the midpoint on each side of the incision and secured to the drapes with clamps This provides excellent exposure and affords additional hemostasis by tamponade The importance of adequate hemostasis has been emphasized by others[4] since even a minimal amount of cutaneous bleeding may obscure the details of dissection In the event that capillary bleeding occurs the blood is quickly removed by irrigation with a few drops of saline and gentle spong ing with gauze Saline irrigation should be used sparingly and quickly absorbed by sponging or else the tissues become edem atous

A 10 to 15 mm segment of the lymph duct is freed of all connective tissue by blunt dissection and 5 0 silk ligatures are placed proximally and distally around it The lymph duct is elevated slightly with the tip of a forceps when the ligatures are passed beneath it in order to prevent twisting or rolling of the lymphatic by contact with the moving silk ligatures Gentle traction on the untied proximal ligature temporarily occludes the lym phatic When the tissues distal to the skin incision are massaged the lymphatic is filled with lymph and becomes distended to several times its original size The distal ligature is tied and both ligatures are se cured to the skin with adhesive tape or clamped to one of the sterile drapes with a hemostat The lymphatic segment is thereby well immobilized for cannulation The point of a small curved cutting needle held in a hemostat is introduced into the

lymphatic between the two ligatures and gently advanced until the broadest portion of the needle has penetrated the lymphatic wall The needle is then partially withdrawn leaving only the tip within the lymphatic lumen With gentle upward traction on the needle the tapered end of the polyethylene cannula containing a stylette is inserted into the opening created in the lymphatic and the needle is then completely withdrawn The proximal ligature is released and without moving the cannula the stylette is withdrawn about 1 or 2 mm Thus the extralymphatic portion of the cannula is rigid and can be maneuvered with good control but the tip is extremely flexible and will yield to the irregular course of the lymphatic lumen without puncturing its wall While the lymphatic is held with a small forceps near the tied distal ligature the cannula is gently advanced until the tip rests in a segment of the lymphatic which has not been disrupted by the dissection If desired the cannula may be advanced even further along the lymphatic lumen by first removing the stylette and gently injecting saline through the infusion extension into the cannula to distend the lymphatic slightly Finally the proximal ligature is tied around the lymphatic and cannula the infusion extension tubing is secured to the patient s skin with adhesive tape and the infusion is started (Fig 2)



Fig 2 [illegible] completed See text for detail

Comment

Inherent differences in the construction of needles and polyethylene cannulae account for the superiority of the latter for intralymphatic injections The needle because it is rigid and sharply pointed cannot easily be threaded along the lymphatic lumen for any appreciable distance without penetrating the lymphatic wall Thus leakage of infused materials is a frequent occurrence when needles are used On the other hand polyethylene cannulae have flexible tips with blunt ends and can be inserted for considerable distances into lymphatics and firmly secured in place thereby eliminating leakage and creating a sturdy preparation These features are of particular importance if chemotherapeutic agents or radioisotopes are to be infused into lymphatics since leakage of these cytotoxic materials may cause marked local tissue reactions which may lead to necrosis[3] Furthermore it may be desirable to infuse these agents over extended periods of time and this arrangement is less likely than a needle to become disrupted before infusion is completed In addition the larger lumen of a catheter permits injection of oily contrast material without the use of expensive equipment and less viscoid materials may be given slowly by gravity infusion Conversely manual or gravity infusion through a small bore needle is virtually impossible

so that elaborate equipment must be employed for that purpose.[4-8,11] Finally we have found this technique of lymphatic cannulation to be simple and more often successfully performed by inexperienced operators than is the method employing small hypodermic needles.

Summary

A technique for lymphatic cannulation using polyethylene cannulae is described which is inexpensive, dependable, and simple to perform. The advantages to the use of cannulae rather than needles are the absence of leakage of infused materials, a more dependable preparation, and greater ease of cannulation and infusion. These features are desirable in lymphatic cannulation for lymphangiography and direct lymphatic cancer chemotherapy.

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Hemodynamic effects of rapid digitalization in experimental cardiogenic shock

*R. F. P. Cronin, M.D., M.R.C.P. (Lond.), F.R.C.P. (C)**
T. Zsoter, M.D., F.R.C.P. (C)
Montreal, Canada

Cardiogenic shock develops in about 14 per cent of patients hospitalized with acute myocardial infarction.[1] Since the outcome is fatal in most of these cases, cardiogenic shock is responsible for approximately one third of the hospital deaths which occur after myocardial infarction.

Digitalization of patients with acute infarction is generally considered to be hazardous or even contraindicated, although sporadic reports have appeared which attest to the safety of digitalis administration under these circumstances.[2-4] It is current practice to restrict the use of digitalis in these patients to those who show evidence of congestive cardiac failure.

Since no experimental data are available on the hemodynamic effects of digitalis in cardiogenic shock, we decided to study the effects of rapid digitalization with acetyl strophanthidin on dogs in experimental cardiogenic shock.

Methods

Twenty-three mongrel dogs which weighed between 14 and 17 kilograms were used. Twenty were anesthetized with intravenous sodium pentobarbital, 30 mg. per kilogram initially, with additional hourly doses of 60 mg. Three animals were anesthetized with intramuscular morphine (2 mg. per kilogram) and intravenous Dial-urethane-Nembutal† (0.25 c.c. per kilogram). All animals breathed 100 per cent oxygen spontaneously throughout the experiment via an endotracheal tube and Collins two-way valve. Arterial blood pressure was recorded via a catheter in the proximal aorta, and left ventricular end-diastolic pressure via a small polyethylene tube introduced transseptally into the left atrium from the jugular vein and maneuvered through the mitral valve. In a separate group of experiments, measurements were also made of right atrial pressure and of peripheral venous pressure, the latter by wedging a fine Teflon catheter with an outside diameter of 0.8 mm. into a distal branch of the forepaw vein. Recordings of pressure were taken at fast speed on a four-channel Sanborn photographic recorder via Statham P23D transducers. Cardiac outputs were measured by injecting weighed quantities of T-1824 dye into the right atrium and recording dilution curves in duplicate, blood being withdrawn from the lower aorta through a

From The M[illegible] G[illegible] [illegible] Medical Clinic, The Montreal General Hospital, Montreal, Canada.
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*Research [illegible] Canadian Heart Foundation. Address: The Montreal General Hospital, 1650 Cedar Ave., Montreal 25, P.Q., Canada.

†Dial [illegible] 100 mg. of Dial, [illegible] 30 mg. of [illegible] barbital per milliliter.

Table I. Effects of acetyl strophanthidin in shocked animals

		Dog number				
		168	*169*	*170*	*171*	*174*
Heart rate (beats/min.)	C	160	124	180	124	148
	S	170	150	160	110	130
	A	162	160	148	116	134
Mean aortic pressure (mm. Hg)	C	113	142	134	118	100
	S	79	93	66	70	86
	A	108	120	106	102	100
Cardiac output (L./min.)	C	2 58	2 57	2 06	3 15	2 60
	S	0 96	1 16	0 75	1 25	1 53
	A	1 89	1 75	1 15	2 26	1 75
Stroke volume (ml.)	C	16 1	20 7	11 5	25 4	17 5
	S	5 5	7 7	4 7	11 4	11 7
	A	11 8	10 9	7 8	19 5	13 1
Total peripheral resistance (units)	C	43	52	59	36	38
	S	71	69	65	52	56
	A	51	60	73	42	57
Left ventricular end-diastolic pressure (mm. Hg)	S	+10	+10 5	+4	+1	−2
	A	0	−1 5	+2	+0 5	−1
Left ventricular stroke work (Gm. M./beat)	C	25 9	40 1	19 9	41 5	24 7
	S	5 0	8 9	3 3	10 6	14 5
	A	18 2	16 5	9 6	27 0	18 6

C, Control before [illegible] embolization. S, Shock 30 minutes after embolization. [illegible] minutes after 0.5 mg. of acetyl str[illegible]
S.D. [illegible]
[illegible] p value [illegible] significant
[illegible]

Gilford densitometer using a constant flow syringe. Total peripheral resistance was calculated as follows and expressed in arbitrary units:

$$TPR = \frac{MBP}{CO}$$

where TPR = total peripheral resistance (units), MBP = mean aortic blood pressure (in millimeters of mercury), and CO = cardiac output (liters per minute).

In 17 animals cardiogenic shock was produced by Agress technique of closed chest coronary embolization using plastic microspheres with a mean diameter of 324 μ during transient acetylcholine arrest and balloon occlusion of the proximal aorta.[4] In 6 control animals sham embolization was carried out using an injection of normal saline during acetylcholine arrest and balloon occlusion of the aorta. In both control and shocked animals procaine amide (100 mg.) was given prior to embolization in order to minimize the risk of ventricular fibrillation.

Pressures were monitored continuously and the cardiac output was determined 30 minutes after embolization. Reductions in arterial mean blood pressure of 35 per cent or greater and in cardiac output of 30 per cent or greater were required as criteria for shock. Rapid digitalization was accomplished in 13 dogs by infusion over a period of 1 minute of 0.5 mg. of acetyl strophanthidin diluted in 10 c.c. of 5 per cent glucose in water. Two dogs received a lower dose of acetyl strophanthidin (0.15 mg.) and 2 others received a higher

Dog number					Average	S D	p
159	160	1	2-3	? 4			
170	140	120	140	180	149	±23 0	>0 4
134	105	134	130	180	140	±24 5	
140	105	176	110	180	138	±34 6	>0 8
150	130	112	124	126	125	±14 9	<0 01
77	90	84	170	60	83	±17 3	
100	100	100	1,2	83	105	±10 1	<0 01
3 6?	2 94	30	3 67	3 51	2 92	± 0 48	<0 01
1 30	1 25	1 13	1 ??	1 20	1 71	± 0 24	
2 07	1 43	1 32	? 55	? 10	1 8?	± 0 40	<0 01
21 3	20 8	20 8	26 2	19 3	20 0	± 4 3	<0 01
9 7	12 0	8 4	1? 2	6 7	9 0	± 2 7	
14 5	13 6	10 5	23 4	11 7	13 7	± 1 5	<0 0?
4	44	45	32	37	43	± 8 0	<0 01
55	68	59	72	42	61	± 9 8	
48	69	61	47	44	55	±10 9	>0 2
+6	+5	+11	−1	+10 5	+5 5	± 4 7	<0 01
−3	−3	−1	−3	−6	−1 6	± 2 2	<0 01
43 8	38 9	33	44 ?	39 3	35 4	± 8 9	<0 01
9 9	14 5	8 3	20 4	4 8	10 0	± 5 3	
20 0	19 1	11 5	39 9	15 5	19 6	± 8 6	<0 02

phanth d ... cases)

dose (2 0 mg) Measurements of pressure and determinations of cardiac output were made sequentially in several animals and the peak action of the drug was found to occur by the eighth minute For purposes of comparison the eighth minute after injection of strophanthidin was chosen as the time for determination of cardiac output in every case

Results

The data obtained from 10 animals subjected to rapid digitalization 30 minutes after the production of cardiogenic shock are summarized in Table I The changes observed in mean blood pressure cardiac output and total peripheral resistance prior to coronary embolization during the shock phase and 8 minutes after digitalization are graphically illustrated in Fig 1 The changes observed at similar time intervals in heart rate left ventricular stroke work and left ventricular end-diastolic pressure are also shown Coronary embolization caused a profound fall in the arterial pressure and cardiac output with a rise in peripheral resistance left ventricular stroke work fell markedly whereas the filling pressure of the left ventricle rose significantly Although the group as a whole showed an average decline in heart rate of 9 beats per minute this was not statistically significant

Rapid digitalization with intravenous acetyl strophanthidin caused a substantial elevation in arterial blood pressure and cardiac output in every animal Rises in pressure and output were roughly propor

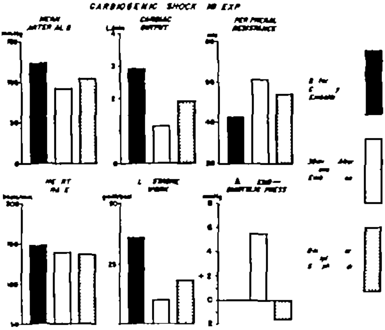


Fig. 1. Mean hemodynamic changes after coronary embolization and the intravenous administration of acetyl strophanthidin in 10 dogs anesthetized with Nembutal.

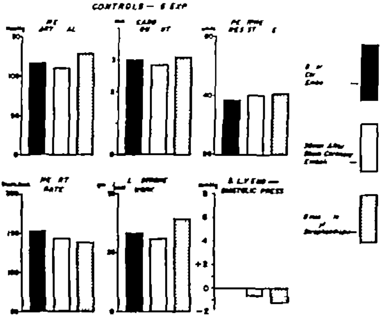


Fig. 2. Mean hemodynamic changes in 6 control dogs after the intravenous administration of acetyl strophanthidin.

tional so that no significant change in calculated peripheral resistance was observed. This restoration of the shocked animals' hemodynamic status toward normal was associated with a marked increase in left ventricular work in all dogs and an average lowering of the end-diastolic left ventricular pressure; there was no appreciable change in heart rate. Other changes in response to the administration of strophan-

thidin which were consistently observed but which are not listed in the table included an increase in stroke volume a widening of the pulse pressure and a more rapid circu lation time As evidence of improvement in myocardial contractility acetyl strophanthidin was found to cause a more rapid upstroke in the arterial pressure pulse with shortening of the systolic duration in every shocked animal Serious arrhythmias did not occur in any of the animals which were given 0 5 mg of strophanthidin although occasional ventricular premature beats developed in 2 Although it is possible that procaine amide masked the potential hazard of acetyl strophanthidin on ventricular irritability this seems to be unlikely in view of the small dose given and the 30 minute interval which was allowed to elapse before digitalization

Furthermore 2 animals which were given a challenging dose of 2 0 mg of acetyl strophanthidin both developed ventricular tachycardia one at 4 minutes and the other at 6 minutes after injection Two animals received a lower dose of acetyl strophanthidin (0 15 mg) which resulted in an effect on all parameters comparable to that in animals which received 0 5 mg of strophanthidin Similarly the response to 0 5 mg of strophanthidin in 3 dogs anesthetized with morphine and Dial urethane Nembutal was essentially the same as that in the animals anesthethized with pentobarbital

The data obtained from the control group of 6 animals are shown in Table II and summarized in Fig 2 It can be seen that no significant change in any of the parameters measured was present 30 min

Table II *Effects of acetyl strophanthidin in control animals*

		Dog number						Average	S D	p
		178	191	193	196	195	2 5			
Heart rate (beats/min)	C_1	196	134	160	120	170	180	152	±32 1	>0 9
	C	200	170	160	130	174	115	142	±32 8	
	A	197	112	168	124	130	110	139	±33 3	>0 9
Mean aortic pressure (mm Hg)	C_1	120	116	112	108	110	128	116	± 7 4	>0 1
	C_4	130	108	120	94	120	90	110	± 5 0	
	A	140	124	126	118	127	137	127	± 7 9	>0 01
Cardiac output (L /min)	C	2 37	3 90	3 82	2 05	3 25	2 58	3 0	± 0 78	>0 7
	C	2 64	3 30	4 2	1 67	3 05	1 80	2 78	± 1 11	
	A	2 79	3 47	5 10	1 98	3 60	2 15	3 19	± 1 22	>0 5
Stroke volume (ml)	C_1	12 1	36 5	23 9	17 1	27 1	14 3	21 8	± 9 2	>0 7
	C	13 2	27 4	26 4	12 8	24 6	15 6	20 0	± 6 8	
	A	14 5	31 0	31 5	16 0	27 7	19 5	23 4	± 7 6	>0 4
Total peripheral resistance (unit)	C	49	28	28	49	34	4	39	±10 3	>0 2
	C_4	46	30	28	49	39	47	40	± 9 1	
	A	46	34	4	56	34	58	42	±13 6	>0 05
Left ventricular end-diastol pressure (mm Hg)	C	—	0	−4	+1	−1	−1	−0 8	± 1 5	>0 3
	A	—	−4	−2	+1	—	+0 5	−1 3	± 2 2	>0 6
Left ventricular stroke work (Gm M /beat)	C_4	20 3	54 0	36 7	24 8	42 4	24 9	33 9	±12 9	>0 6
	C	2 9	42 9	41 7	15 3	42 3	18 8	30 7	±13 0	
	A	26	45 7	5 0	25 5	49 2	35 3	39 9	±11 5	>0 2

C C4 and C Thirty [illegible] of [illegible] base stable [illegible] A Eight [illegible] after 0.5 mg of acetyl strophanthidin intravenously
S D Standard deviation
** p value highly significant.

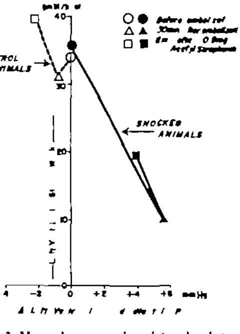


Fig. 3. Mean changes in the relationship between left ventricular end-diastolic pressure and stroke work after coronary embolization and digitalization in control and shocked animals.

utes after sham embolization. This indicates that the administration of procaine amide and acetylcholine and transient balloon occlusion of the aorta do not contribute to the hemodynamic features of shock exhibited by the animals embolized with microspheres. After the administration of acetyl strophanthidin, the only significant hemodynamic change observed in the control group was a rise in mean blood pressure. Although a small increase in cardiac output and an increase in left ventricular work were observed in every animal, the changes were not statistically significant. No alteration in heart rate occurred and no cardiac arrhythmia was observed; neither was there any consistent change in the character of the arterial pressure pulse contour.

When left ventricular stroke work is plotted against alteration in left ventricular end-diastolic pressure in the control animals, a slight positive inotropic effect is evident after digitalization, which indicates increased work performance by the left ventricle for a reduced filling pressure (Fig. 3). In the shocked animals coronary embolization has a marked negative inotropic effect, increased filling pressure being associated with reduced left ventricular stroke work. This distorted relationship is substantially corrected by strophanthidin, which indicates a powerful positive inotropic effect.

An increase in pressure in the small peripheral vein occurred in 7 out of 10 dogs at 5 minutes after the administration of acetyl strophanthidin (mean rise of +2.7 mm. Hg).

Discussion

The difference between experimental coronary embolization with microspheres in healthy dogs and coronary occlusion in patients is evident. Nevertheless, the hemodynamic features of the resulting cardiogenic shock are quite similar, i.e., a marked decrease in systemic blood pressure, cardiac output, and left ventricular work, with an increase in peripheral vascular resistance and prolongation of the circulation time. Consequently, it is thought that this experimental preparation is suitable for the study of cardiogenic shock.

This study has shown that the rapidly acting digitalis, acetyl strophanthidin, is beneficial in controlling cardiogenic shock. Although years ago McMichael[4] suggested that the primary effect of digitalis is on the peripheral veins, it now seems to be well established that the principal effect is on the heart and that other hemodynamic changes are secondary to this.[7] The positive inotropic effect of strophanthidin has been well demonstrated in this study, as indicated by the increase in cardiac output and left ventricular work, the decrease in left ventricular end-diastolic pressure, and the shortening of systolic duration. However, the immediate increase in arterial pressure which consistently occurred in our shocked animals soon after or even during the intravenous injection of acetyl strophanthidin cannot readily be explained as a consequence of the increased cardiac output alone. Indeed, in animals in which several determinations of cardiac output were made during the first 10 minutes after digitalis, the increase in blood pressure clearly preceded the increase in cardiac output (Fig. 4). This immediate increase in pressure would probably best be explained by vasoconstriction caused by acetyl strophanthidin.

Such an effect is in accord with several reports which indicate that digitalis preparations including acetyl strophanthidin cause constriction of systemic arteries and of veins.[8,10] Thus arterial constriction could be partially responsible for the increase in blood pressure which occurred after the administration of acetyl strophanthidin in our experiments.

Acetyl strophanthidin increased the pressure in the small peripheral vein 5 minutes after injection in 7 out of 10 dogs. Since right atrial pressure was no higher at that time, this resulted in a greater pressure gradient between the small veins and the right heart which may have promoted an increase in venous return. This may be an additional factor in explanation of the beneficial effect of digitalis in the case of shock. Although the effect of digitalis on pressure in larger veins has been reported, the effect on pressure in the small veins has not been studied previously. Since the pressure in the small veins increased before that in the right atrium became lowered,

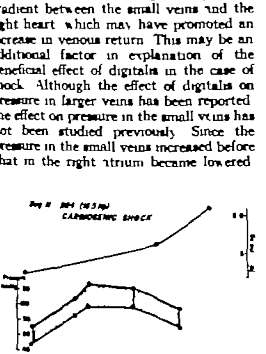


Fig. 4. Serial changes in cardiac output and in pressures at several sites after intravenous acetyl strophanthidin 30 minutes after coronary embolization.

our results do not support the hypothesis of a sphincter-like constrictor effect of digitalis in the larger veins but suggest a generalized venoconstrictive effect.

The value of a rapidly acting digitalis preparation in the treatment of human cardiogenic shock can be established only in patients. This is usually regarded as hazardous, and Goodman and Gilman[1] state that digitalis is contraindicated in these patients unless there is congestive heart failure. This opinion is based on the fact that the irritability of the heart is increased after myocardial infarction and the incidence of digitalis induced arrhythmias is higher. The experimental evidence such as the work of Travell and associates,[11] which supports this, however, is based on dosages that are considerably larger than those commonly employed therapeutically. Indeed, some reports on human beings with myocardial infarction emphasize the safety of digitalis administration. Askey[1] found no increased incidence of arrhythmias in 50 patients treated with digitalis as compared to 50 untreated patients.

In the majority of our experiments 0.5 mg. of acetyl strophanthidin, a rather large dose, was used, whereas 2 dogs received a smaller dose (0.15 mg.) with similar beneficial effects. Consequently, it is thought that a reconsideration of acetyl strophanthidin for the treatment of human cardiogenic shock seems to be warranted.

Summary

Cardiogenic shock was produced in dogs by closed chest coronary embolization with plastic microspheres. Rapid digitalization with acetyl strophanthidin caused a significant rise in arterial blood pressure, cardiac output, and left ventricular stroke work, and a reduction in left ventricular end-diastolic pressure in the shocked animals.

The only significant effect of acetyl strophanthidin observed in a group of control animals was a rise in the arterial blood pressure. Although the positive inotropic action of this drug can be readily demonstrated, it is suggested that the hemodynamic effects in cardiogenic shock are due not only to its inotropic but also to its peripheral vasoconstrictor effect.

The results of this investigation suggest

that the use of digitalis glycosides in the treatment of clinical cardiogenic shock deserves further exploration

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Effect of site of injection upon left ventricular indicator-dilution output

*Philip Samet, M.D.**
William H. Bernstein, M.D.
Aaron Medow, M.D.
Miami Beach, Fla.

The indicator-dilution cardiac output technique has gained wide acceptance. The most common site of injection is the peripheral venous system or the right heart. The current approach to measurement of true pulmonary blood volume[1-4] involves the introduction of indicator into the pulmonary artery and left atrium in rapid succession with systemic arterial sampling after both injections. The difference in mean transit times multiplied by the cardiac output is equated with pulmonary blood volume. An indirect method for estimation of bronchial blood flow involves the injection of indicator into the right atrium with simultaneous pulmonary and systemic arterial sampling as representative of right and left ventricular output, respectively.[5] If the latter is larger than the former, the difference is equated with bronchial blood flow. Underlying all these methods is the assumption that valid measurements of left ventricular output may be made via injection of indicator into the right heart chambers. Abelmann[6] has suggested, however, that the systemic arterial indicator-dilution curve may be distorted by undetected early recirculation after injection into the right heart. Such deformation would increase the area under the dye curve and result in underestimation of left ventricular flow. The purpose of this report is to compare systemic arterial indicator-dilution curves after injection into the left atrium and the pulmonary artery in rapid succession. If no systematic differences are observed between these sites of injection, it can be concluded that valid determinations of left ventricular indicator-dilution output may be made via sites of injection in the right heart chambers.

Materials and methods

These observations were made in the course of transseptal left heart catheterization in a group of patients with predominantly rheumatic heart disease. Congenital heart disease without right-to-left or left-to-right shunts was present in a few patients. A few subjects were found to be free of heart disease after study. One hundred ten paired observations were made in patients with sinus rhythm. Atrial fibrillation was present in another group of 59 patients.

Indocyanine green dilution curves were inscribed from a systemic artery via a Gilford densitometer. A Harvard constant withdrawal infusion unit was employed

From the Cardio-Pulmonary Laboratory of the Department of Medicine, Mount Sinai Hospital, Miami Beach, Fla., and the Section of Cardiology, University of Miami School of Medicine, Coral Gables, Fla.
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*Address: Mount Sinai Hospital of Greater Miami, 4300 Alton Rd., Miami Beach 40, Fla.

All blood withdrawn was reinfused after completion of inscription of the indicator curve on an 8 channel photographic Elec tronics for Medicine recorder Injections of indocyanine green were made into the left atrium and pulmonary artery within 2 minute intervals of one another

Results

In the 110 patients with sinus rhythm the cardiac indices after injections into the pulmonary artery and into the left atrium averaged 2 78 and 2 73 L per minute per square meter respectively The difference is statistically significant (0 01 > p > 0 001) but is of little clinical importance In the group with atrial fibrillation the average cardiac indices were 2 01 and 2 01 respectively (0 9 > p > 0 8) (Table I) The differences between the pulmonary arterial and left atrial injection sites for both rhythms are randomly distributed about the zero dif ference point (Fig 1) The per cent differ ences in Fig 1 represent the differences between the left atrial and pulmonary arterial injection site outputs divided by the mean of the two outputs

Discussion

The data in the present study clearly demonstrate that left ventricular indicator dilution output curves obtained via a systemic arterial sampling site provide equally valid output values regardless of whether the site of injection is in the pul monary artery or in the left atrium Yu[4] Varnauskas Milnor[1] and Dock and associates have reported similar observa tions using methods comparable to those employed in the present study Milnor and Yu employed indocyanine green as the indicator injected successively into the left atrium and pulmonary artery Varnauskas utilized injection of bromsulfophthalein and indocyanine green simultaneously into the pulmonary artery and left atrium respectively Dock introduced Evans blue and I[131] labeled serum albumin into the pulmonary artery and left atrium re spectively On the other hand Abelmann and Ryan[6] have published data suggesting that the injection of indicator into the right heart with systemic arterial sam pling underestimates left ventricular out

Table I Effect of site of injection upon left ventricular indicator dilution output (liters per minute per square meter)

Catheterization number	PA	LA
A Normal Sinus Rhythm		
617	2 95	2 73
625	2 75	2 69
632	2 75	2 91
639	1 88	1 94
643	2 64	2 6
650	2 33	2 28
665	3 58	3 74
667	2 58	2 81
687	2 62	2 58
701	2 19	2 36
721	2 90	89
726	3 2	3 31
733	2 55	2 23
743	3 19	2 97
753	3 15	3 08
756	2 76	2 61
757	3 93	3 59
765	2 86	2 51
771	2 91	2 9
774	4 80	4 05
7 6	1 45	1 51
778	2 63	2 54
783	2 75	2 52
786	2 75	3 01
787	3 04	2 76
789	3 15	3 13
791	3 11	3 08
794	2 81	2 78
97	2 67	2 60
802	2 30	2 18
804	1 34	1 30
803	3 81	3 11
815	4 32	3 14
816	2 35	2 05
826	3 57	3 40
829	3 45	3 47
831	2 45	2 31
832	1 63	1 50
838	2 02	1 97
846	2 20	2 33
848	3 54	3 34
851	2 53	2 35
853	2 00	1 86
855	2 90	2 91
857	2 44	2 48
858	2 27	2 32
859	4 28	3 99
865	1 97	1 90
868	3 09	3 04
869	2 96	2 96
8 0	3 62	3 58
873	3 12	3 34
877	4 12	4 02
878	2 11	2 29
879	1 78	1 88
881	2 89	2 99
886	3 90	3 84

Table I —Cont d

Catheterisation number	*PA*	*LA*
892	1 42	1 28
893	2 73	2 68
894	2 23	2 34
897	3 07	3 07
898	1 87	1 94
902	2 57	2 68
904	3 44	3 52
909	3 24	3 38
910	3 22	3 05
911	2 22	2 21
912	2 93	2 62
913	2 77	2 71
915	1 67	1 55
916	3 24	3 30
919	4 37	4 28
921	3 30	3 14
929	2 26	2 33
936	3 46	3 46
939	2 05	2 08
940	4 28	4 01
945	2 31	2 03
952	1 46	1 52
953	2 95	3 00
954	2 39	2 45
959	3 89	3 77
960	2 36	2 55
963	2 84	2 68
966	3 46	3 53
967	2 93	2 85
969	3 29	3 19
970	3 15	2 95
979	3 23	3 31
980	3 49	3 34
982	2 95	3 12
984	3 27	3 04
985	3 33	3 05
990	2 09	2 07
996	2 38	2 35
997	2 62	2 57
999	1 51	1 34
1006	3 42	3 26
1013	2 38	2 24
1020	2 24	2 30
1024	2 06	2 00
1026	2 03	14
1029	3 6	3 50
1031	1 71	1 94
1033	2 63	2 90
1034	2 22	2 23
1036	2 51	2 68
1038	3 10	3 31
1040	2 31	28
1041	2 69	2 43
Mean	2 78	2 73
B Atrial Fibrillation		
670	1 76	1 78
639	2 03	2 02

Table I —Cont d

Catheterisation number	*PA*	*LA*
663	2 05	1 88
684	1 75	1 87
690	2 25	1 90
694	2 71	2 85
713	1 75	1 56
761	1 81	1 83
762	2 07	1 94
767	2 14	2 32
782	1 24	1 46
785	1 64	1 73
792	1 88	1 86
798	2 95	2 76
800	2 20	2 01
803	1 68	1 66
809	1 34	1 18
817	2 59	2 63
820	1 54	1 66
821	2 38	2 52
835	1 73	1 74
836	1 50	1 31
839	1 67	1 63
849	1 72	1 93
852	2 17	2 23
856	2 49	2 72
860	1 74	1 67
862	1 57	1 58
863	2 59	2 46
867	2 22	2 33
874	2 37	2 41
880	2 20	2 20
882	1 94	1 96
887	1 72	1 67
890	2 58	3 00
900	2 01	1 89
901	1 35	1 37
917	2 40	2 32
923	2 28	2 31
924	2 37	2 46
930	1 71	1 69
932	1 69	1 64
935	1 75	1 78
941	1 88	1 63
947	1 32	1 36
950	1 75	1 89
951	1 70	1 69
964	2 78	2 76
971	1 23	1 34
974	11	2 18
975	2 68	2 64
977	2 35	2 33
987	2 1	2 45
992	2 51	2 44
1005	1 26	1 24
1009	1 93	1 98
1017	2 37	2 1
1019	2 14	1 97
1030	2 76	2 58
Mean	2 01	2 01

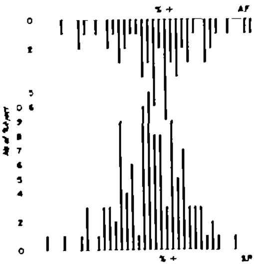


Fig. 1. Per cent difference between left atrial and pulmonary arterial injection for the group of patients with sinus rhythm (S.R.) and atrial fibrillation (A.F.), respectively.

put. Two lines of evidence were advanced. First, the injection of indicator (Evans blue or indocyanine green) into the superior vena cava with simultaneous sampling from the pulmonary and brachial arteries resulted in significantly higher right than left ventricular outputs. Secondly, injection of Evans blue into the left atrium with sampling from the brachial artery, followed by injection of indocyanine green into the right atrium, again with sampling from the brachial artery, resulted in significantly higher outputs from the former site of injection. Abelmann postulated that traversal by injected indicator of the right heart and pulmonary bed in addition to the left heart resulted in undetected early recirculation, with subsequent overestimation of the area of the dilution curve and underestimation of the resulting calculated output. These observations have caused Fritts[5] to doubt that bronchial flow may be measured as the difference between left and right ventricular indicator-dilution outputs after injection into the right atrium or superior vena cava.

It is our belief, however, that Abelmann's data are not in accord with extensive published and unpublished data. More than 1,000 simultaneous pulmonary and systemic arterial indicator-dilution curves (after injection into the superior vena cava or right atrium) have been recorded in our laboratory.[7] Systematic differences between right and left ventricular outputs have not been observed. Right ventricular output was not greater than left ventricular output. The present studies illustrate that injected indicator may traverse the pulmonary bed and left heart and still result in output levels similar to those obtained after only the left heart is traversed, i.e., similar systemic arterial indicator outputs may be obtained after pulmonary arterial as well as left atrial injection. Similar data have been published by other observers in the course of studies of pulmonary blood volume. Determination of left ventricular output by systemic arterial sampling after injection into the right heart rests on solid ground.

Summary

The injection of indicator into the pulmonary artery and left atrium, with systemic arterial sampling, resulted in similar levels of output. The flow levels after injection into the left atrium were not higher but, on the contrary, were somewhat lower than those after injection into the pulmonary artery. These data validate the assumption that measurements of left ventricular output may be made via injection of indicator into the right heart.

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Observations on the localization of tritiated digoxin in myocardial cells by autoradiography and ultramicroscopy

With added reference to the sarcotubular system studied by cell fractionation and enzyme staining

*Harry A. Fozzard, M.D.**
*John R. Smith, M.D.***
St. Louis, Mo.

The mechanism of the beneficial effects of digitalis on cardiac contractility is obscure.[1] With the recent increase in our knowledge of the sources of energy within cells, numerous investigations have been concerned with the effects of the glycosides on the oxidative and electron transport mechanisms of the mitochondria.[2,3] In addition, it has been noted that digitalis influences the actin-myosin protein complex,[4,5] which is thought to be the structure directly responsible for cardiac work, and that the cardiac active glycosides alter sodium and potassium transfer mechanisms in erythrocytes.[7] Recent experimental evidence likewise has indicated the presence of an enzyme system in the membrane and sarcotubular fraction of the myocardium that is strongly influenced by concentrations of sodium and potassium and is inhibited by digitalis in physiologic doses.[8,9] Therefore, there is little agreement as to which subcellular structure is involved in the digitalis action that results in improved myocardial function when the heart is in clinical failure.[1]

In an attempt to locate more precisely the subcellular site(s) of action of the digitalis glycosides, we first employed the technique of autoradiography combined with electron microscopic examination of hearts digitalized with tritium-labeled digoxin.[11] In order to resolve certain problems resulting from the autoradiographic findings and to locate the digoxin more exactly, other morphologic and biochemical studies were likewise performed.

Methods

The method for preparing autoradiographs of the H^3-digitalized cardiac muscle has been presented in detail previously.[11] Only a brief description of this procedure will be given. Bullfrog hearts were perfused in vitro with Ringer's solution, to which tritiated digoxin (66.4 μc/mg.) was added. Muscle strips were taken for electron microscopic preparation after digitalis in-

F[illegible] Card[illegible] D[illegible] Departm[illegible] of M[illegible] W[illegible] U[illegible] University School of Medicine, St. Louis, M[illegible]
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Received for publication May 29, 1964.
[illegible] Research Department of Medicine, W[illegible] University [illegible] University of Bern, Bern, Switzerland, 1963-196[illegible]
Address: Department of [illegible] Medicine, W[illegible] University School of Medicine, [illegible] South Kingshighway, St. Louis, Mo. 63110.



Fig. 1. Autoradiograph of tritiated digoxin mixed with NTB emulsion and exposed for 4 days and developed. × 14,000.

toxication was evident. In other experiments Starling heart-lung preparations of dogs were similarly digitalized. Small pieces of ventricular muscle were removed before fixation if enzymatic studies were to be made. Digoxin is virtually insoluble in acetone; therefore, the specimens were fixed for 30 minutes in 50 per cent acetone and 10 per cent formalin and for 90 minutes in buffered 1 per cent osmium tetroxide. Tissue dehydration was then accomplished by successively increasing concentrations of acetone, with final embedding in 70 and 30 parts of butyl methyl methacrylate, respectively.

Thin sections on 200 mesh steel grids coated with Formvar were dipped in liquid emulsion (Eastman Kodak NTB 3) and were exposed in light-tight boxes for 10 to 12 days. After the grids were developed, the emulsion gelatin was removed by emersion of the grids in 0.1N sodium hydroxide for 1 hour.[12] After this treatment, the cellular details with superimposed silver grains from the tritium disintegrations were clearly apparent in the RCA EMU 3 electron microscope.

Because the autoradiographic technique could not distinguish between glycoside localization in the myofibrils and in the immediately adjacent sarcotubular system, two techniques were employed to attempt a more precise differentiation. The first procedure entailed staining for the sodium-potassium ATPase enzyme system with lead salt in the sections, using the method reported by DeBeyer, DeMan, and Persijn.[13] The sections were then examined with the electron microscope for localization of the lead deposits. The second procedure required a separation of cellular particles from digitalized hearts by ultracentrifugation. Although it is possible to obtain a fraction that is composed predominantly of sarcotubular structures and is free from actomyosin,[9,14,15] much of the sarcotubular structures are sedimented in earlier fractions. An assay for Na-K ATPase was used as an indicator of the quantity of sarcotubular structure present in the

fractions.[8] This measure could be compared with the radioactivity from the digoxin in each fraction.

Results

Losses of H^3 digoxin during tissue preparation for electron microscopy. The principal problem to consider for the autoradiographs was the loss of about one quarter of the H^3 digoxin from the tissue during the fixation-dehydration procedure. Probably the H^3 digoxin in the extracellular spaces of the tissue block escaped during preparation. By assuming that the extracellular space is 30 per cent of the tissue volume and that the concentration of isotope in this space is the same as in the perfusing fluid, one can estimate the quan

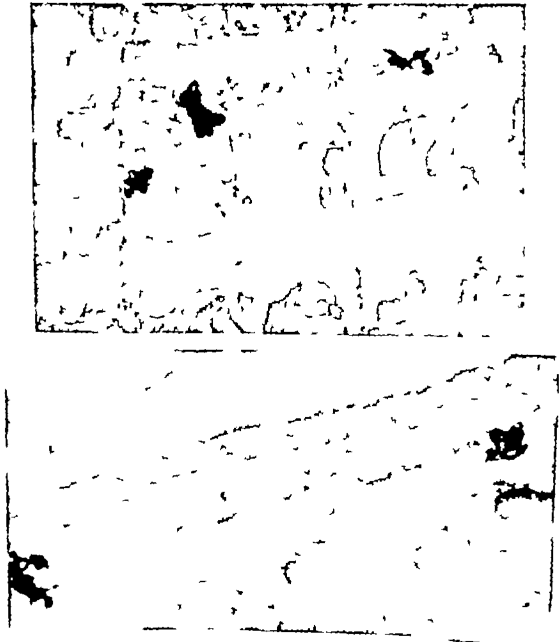


Fig. [illegible] Autoradiographs of [illegible] myocardium showing typical sites of localization of tritiated glycoside [illegible] A band of m[illegible] [illegible] the Z bands. Above ×14 000. Below ×28 000.

tity of radioactivity present in that space when the tissue was removed from the animal. This calculated value was approximately the same as the total losses during tissue preparation, which suggests that these losses could have come from the extracellular space[11] and that the remainder was fixed in some way by the tissue.

Autoradiographic observations. The autoradiographs are clear, and the tritium-exposed emulsion grains can be distinctly seen. Fig. 1 illustrates the emulsion exposed by H^3 digoxin without tissue. It was assumed that the center of the silvered area represented the most likely site of tritium emanation (or site of the glycoside molecule). A developed silver grain was frequently one half micron in diameter and of characteristic form. Because of the low concentration of the glycoside in the muscle, only single silvered areas (presumably exposed by single molecular disintegrations) could be seen. It was rare to observe more than one in each myofibrillar sarcomere. Consequently, a quantitation of the results could be made only by counting the frequency with which the exposed silver grains were associated with a cell structure. Typical fields are shown in Fig. 2. The majority of the silver grains were observed over the A bands of the sarcomere (60 per cent) or over the edges of the Z lines (25 per cent). Exposed areas on the membrane of cell surfaces were uncommon. Only rare localization was noted in cell nuclei or mitochondria. It seems probable that this localization of grains could not have resulted from random distribution within the cells, since the pattern was recurrent in the numerous sections examined. No conclusion could be drawn from these micrographs as to whether the radioactivity originated in the actomyosin portion of the sarcomere or in the closely related sarcotubular system. In order to investigate the problem of glycoside location more completely, the ultracentrifugal separation of cell particles was employed.

Ultracentrifugal distribution of H^3 digoxin and Na-K ATPase. The separation of subcellular structures by ultracentrifugation is crude at best. Nevertheless, by this method it is possible to obtain a fraction that contains primarily membranes and sarcotubular structures, as shown by electron microscopy.[11,12] However, with even the best preparations, much of the membrane material (and simultaneously Na-K ATPase activity) remains in the heavy sediment as part of whole or partially broken cells. On the assumption that the Na-K ATPase activity is a measure of the quantity of sarcotubular structures present in an ultracentrifugal fraction, a comparison can be made with the quantity of radioactivity from the H^3 digoxin in this and other fractions of the cells. Table I shows the quantities of radioactivity and Na-K ATPase activity in the various cell fractions. Although the bulk of the H^3 digoxin appears to be in the heavy sediment fraction, the enzyme measurements suggest that an equivalent amount of

Table I. Comparative quantities of radioactivity and of the Na-K ATPase enzyme activity in cellular fractions separated by ultracentrifugation

Fraction	Experiment 1		Experiment 2		Experiment 3		Average	
	H^3	Enzyme	H^3	Enzyme	H^3	Enzyme	H^3	Enzyme
Whole cells, [illegible] (1 1	81	71	57	71	6[illegible]	77	[illegible]	74
Supernatant (5 ?)	3	17	33	5	17	5	18	9
Membranes and sarcotubular structures (1 2)	13	12	10	21	1	18	13	17

Values are expressed as percentages of [illegible] radioactivity or enzyme activity.



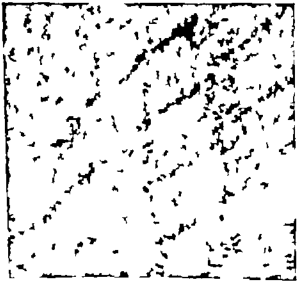


Fig. 3. Micrographs showing lead stains for ATPase especially dense along cellular membranes and the Z bands of myofibrils (see text). *Above* ×ca 5 000. *Below* ×ca 10 000

membranous material was present. In general the Na-K ATPase values follow the radioactivity closely. In Experiment 2 it is likely that the tissue was not sufficiently washed before grinding thereby leading to a high value of radioactivity in the supernatant arising from the extracellular fluid in the tissue. In Experiment 3 the protein contents of the fractions were measured and the counts and enzyme activity per milligram of protein were both four times higher in the final centrifugal fraction than in the homogenate or in the first heavy sediment containing portions of sarcomeres. The myofibrils and actomyosin should have been entirely present in the heavy sediment because of their insolubility in 0.25M sucrose at pH 7.4. The similarity of distribution of the H³ digoxin and the Na-K ATPase in the second fraction then raised the possibility that the glycoside was more probably related to the sarcotubular system than directly to the actomyosin. It should be mentioned that some of the Na-K ATPase activity may have been inhibited by the radioactive digoxin already present; however, this should not have been large because the enzyme solutions were diluted more than a hundred fold before assay. Comparison with previous attempts to localize intracellular digitalis by centrifugal separation is difficult because of differences in technique.

Na-K ATPase stain. An attempt was made to demonstrate the distribution of the Na-K ATPase morphologically by the staining procedure. Fig. 3 shows these results indicating that the distribution of the enzyme is almost exclusively on the surface membranes and the Z lines. This result agrees with those of DeBeyer, De Man, and Persijn.[18] The enzyme does not coincide in distribution with digoxin as seen on autoradiographs. It suggests that the enzyme and the glycoside are not at the same intracellular location. This technique, however, depends on the diffusion in vitro of lead from the extracellular space. The equilibrium would therefore not be so complete in the more distant intracellular compartments such as the longitudinal part of the sarcotubular system. This objection casts some doubt on the result. A fuller understanding of the techniques may permit a better explanation in the future.

Discussion

The autoradiographic observations clearly point to a localization of the H³ digoxin in or near the sarcomere units of the myocardial cell. There is almost a total absence of radioactivity in the mitochondria or nuclei or on the surface membrane. In an interesting report, Tubbs, Wheat, and Crevasse[19] also described localization of H³ digoxin by an autoradiographic technique with the electron microscope. They reported a predominant distribution of the radioactivity in the region of the A bands. In addition they found some 20 per cent of activity in the mitochondria. This difference in their results and ours is unexplained. However, these investigators used alcoholic dehydration of their tissues, which we had found extracted most of the glycoside during preparation. One questions whether the use of ethanol may have provoked displacement of some of the intracellular digoxin.

The apparent concentration of H³ glycoside at a given intracellular site does not necessarily prove that the substance acts at that site, for its distribution may be determined by such factors as solubility or protein binding. On the other hand, when one considers the proportionately small number of glycoside molecules that produce a striking pharmacologic effect, it seems probable that the site of intracellular action is represented by the point of binding in this case. A redistribution of the H³ digoxin may have taken place during tissue preparation, although care was taken to avoid this possibility.

Although the primary relationship of the radioactivity to the sarcomere is demonstrated, this does not prove entirely the subcellular structure with which the digoxin is associated. The discrimination of silver grains in our autoradiographs was probably not greater than one micron.[20] The longitudinal portions of the sarcotubular system lie along the myofibrils of the A band; the transverse sarcotubular components are aligned along or near the Z bands. The autoradiographs could not distinguish between structures so closely related as the

tubules and the myofibrils. Although the myofibrils may be the site of digitalis activity, there is ample reason to consider the possibility of localization in the adjacent sarcotubular system.

One possible means of distinguishing the myofibrils or the sarcotubular system as the localization sites of digoxin resides in the identification of the tubular system by its distinctive Na-K ATPase activity. The technique for separating sarcotubular particles and that for preparation of Na-K ATPase are quite similar.[11, 9] Furthermore, the electron microscopic pattern of the enzyme-containing fraction is predominantly of sarcotubular structures.[9, 11, 12, 13] The enzyme activity appears to be firmly bound to the tubular particles[11] and is inactivated when treated with desoxycholate.[1] In these experiments the ultracentrifugal distribution of H^3 digoxin and that of Na-K ATPase activity were similar. In addition, the high-speed sediment contained a fourfold concentration of radioactivity and enzyme activity per milligram of protein over the values found in the whole muscle homogenate or the heavy sediment fraction. A close relationship between the digoxin and the sarcotubular system is apparent, and the implications for such a site of digitalis localization must be considered.

The effect of the digitalis glycosides on myocardial contractile strength may be on the fibril (actomyosin) or on the sarcotubular system. The central role of actomyosin in the contraction process is clear. However, attention has been focused on the sarcotubular system as the organelle for excitation-contraction coupling and for the regulation of intracellular Ca++ concentration.[15, 4] The many reasons for considering the Na-K ATPase enzyme system itself as the site of action of digitalis have been recently summarized, and a temporal correlation has been demonstrated between the effects of digitalis on the loss of cellular potassium and the inotropic action.[16] The present studies indicate that the glycoside is certainly present at the sarcomere level and suggest the sarcotubular system as the locale of action. Recently Lee[7] was able to demonstrate an effect of digitalis on a glycerinated muscle preparation. This effect was present only as long as a relaxing factor remained in the preparation. Since relaxing factor activity appears to originate or reside in the sarcotubular system,[8] Lee's experiments afford additional evidence that the sarcomeric sarcotubular system may be the primary intracellular site of action of digitalis glycoside.

Summary

The intracellular localization of tritiated digoxin was studied by an autoradiographic technique using the electron microscope. The radioactivity was found to be closely associated with the myofibrillar sarcomere. An attempt was made to separate the myofibrils and actomyosin from the closely related sarcotubular system by means of ultracentrifugation. A comparison of the resulting distribution of the radioactivity to the Na-K ATPase (used as a measure of the sarcotubular system) suggested that the cardiac glycoside is associated with the intracellular sarcotubular system rather than with the actomyosin.

We are indebted to Dr. Stanley M. Bloomfield of Burroughs Wellcome & Company, Inc., for the provision of the tritiated digoxin that made possible this work. We are likewise grateful to Dr. William H. Daughaday, of the Department of Medicine, for the use of scintillation counting equipment.

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Case reports

Myocardial infarction, gram negative bacteremia, prolonged shock, and leukemoid reaction

Frederick B. Watts, M.D., F.A.C.P.
Detroit, Mich.

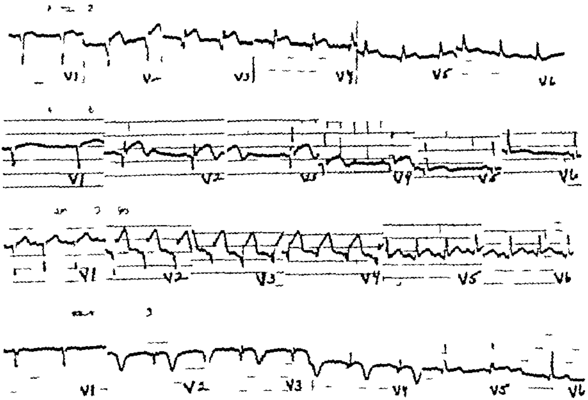
Shock, whether cardiogenic or bacteremic, has never been adequately defined and the etiology never completely explained, although a reduction in cardiac output seems to be characteristic of both.[1,2] This case is presented because of two separate predisposing causes of prolonged hypotension, myocardial infarction as well as gram negative bacteremia. The onset without fever or anginal pain is unusual, as is also the psychotic reaction and convulsion with tremors preceding the shock state. Of special interest is a leukemoid reaction with a precipitous rise in the white blood count to 73,750 per cubic millimeter after the use of vasopressor drugs. This is unusual in gram negative bacteremia but has been attributed to the use of metaraminol bitartrate.[4] The hypotensive state persisted for 31 days. The cause of the convulsive seizure is unknown.

Case report

This 68-year-old white man, a retired minister, was admitted to St. John Hospital on Aug. 1, 1963, complaining of severe weakness of 1 week's duration, no bowel movements for 5 days, and inability to eat for 2 days. The history was actually given by his wife since the patient was uncommunicative and completely withdrawn as he lay on his right side with his feet drawn up in the fetal position. His past health had been excellent, and he had been able to hunt all day and walk for long distances. Approximately 6 months prior to admission, while in Arizona, he noticed some urgency and hesitancy in urination which progressed until while in San Diego in early May he was unable to void and had to be catheterized twice. An indwelling catheter was inserted on the second occasion. He then decided to return to Detroit where he was admitted to Cottage Hospital on May 26, 1963, for a suprapubic prostatectomy on May 28. Two weeks after operation he began to have severe anginal pain. Two cardiograms were normal but a third 1 week after onset of anginal pain suggested myocardial ischemia. His convalescence was otherwise normal and he was discharged 4 weeks after admission with a prescription for potassium iodide solution three times a day. At home his slow convalescence was characterized by anorexia, constipation, and general weakness. He also complained of gaseous distention and obstipation. His worry about intestinal obstruction led to his admission to St. John Hospital for study. Examination at this time revealed a weak, malnourished, elderly man who was quite uncommunicative and appeared to the resident staff to be psychotic. The pupils were equal and normally reactive; optic fundi showed Grade 2 arteriosclerotic changes with narrowing and nicking of vessels but no hemorrhages or exudates and no papilledema of the optic discs. The neck was normal with no adenopathy; the chest was symmetrical with clear lung fields, and the heart was of normal size with sinus rhythm and no murmurs. The pulse was 80 and the blood pressure was 110/70 mm. Hg. There was no abdominal distention, no organomegaly or masses, but the abdominal aorta appeared to be enlarged and firm. The extremities appeared to be normal.

At 7:30 A.M. on the day after admission and after a quiet night he suddenly complained of occipital headache, tightness in the chest, and then went into a generalized convulsive seizure that was followed by coarse tremors of the right arm and leg and horizontal nystagmus with quick com

From the Department of Internal Medicine, St. John Hospital, Detroit, Mich.
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Reprint requests should be addressed to: Dr. Frederick B. Watts, M.D., [illegible] South Oxford Road, Grosse Pointe 36, Mich.



F 2 El t rd gr m rec rded different day See text

t c t the ri ht. The m ement w re inv lu tary f n few minutes h skin bec me a hen d p le the b d pres ure fell t 60 40 mm. Hg d the pulse n reased t 170. The body temper t t w 99 F. The deep ten ion reflexes ere ased the ht nd tremor of the right m l leg pe ted f r l h u. There w tran ient pha ia f r l hour. H remained nscious nd one t l d ppea d t have decreased muscle trength the left. The medical re lent in tituted ox ge ther p p n h mpres on f pos ible cerebr v la d t nd myocardial infarc tion. At 40 a.m. the blood pres ure w 90/60 mm. H t the e w t ll a hen nd the kin w l d m t. At 8:30 a.m. the bloo l pres ure was 0/40 mm. H there w no residual tremor and reflexes wer normal ith neg tive Babin ki n

At 8:30 a.m. 40 mg. of Solu-Medrol w ad led to the intr enou h ose that w running and metaraminol had t be ont nued every 30 minutes because the blood pres ure n tenths below 90 mm. H t r nd 50 mm. Hg dia tolic. At 9:05 a.m. the bl od pres ure f ll t 40/0 mm. H and the l w gray d lammy so that levarterenol wa tarted intraven l with two ampules per 1,000 c.c. of gluc se solution. The patient at th time experienced severe chest pain. An ECG was taken on the ba of which diagnosis of acut anteroseptal infarct on w ma le nd heparin was started i tra en u m d led d ses. At 10:30 a.m. the bl l press re rose t 110 m m. Hg sy tolic nd the patient was ble to v id 340 c.c of urine. Throughout the day his condition re mained critical but lor was ashen and the urinary output was scanty.

During Aug. 3, 1963, the blood pressure remained t hock levels and le rterenol was increased t four ampules; the next d y it wa again increased to six mpules n order to permit lower drip of glucose solutio Solu-Cortef, 100 mg. was also added to the intra n us infusion of glucose. The hem globin wa 14 Gm. on August 2 with a white blood count of 20,000 per cubic millimet with N 78, band 19, L3 with hematocrit 43 volumes per cent. On Augu t 3 the white blood count rose to 2 50 per cubic millimeter with N65, band 27, L4, M1, metamyelocyt 3. The urine had a pecific gravity of 1.007 acid with albumin 2+, 90 to 100 red blood cell 15 to 20 white bl od cell and b c teria 4+. Urine and blood culture were taken and because bacteremia wa su pecte l the patient was tarte l n D cy lin (penicillin 400,000 units —streptomycin 0.5 Gm.) every 6 hours. On Augu t 8 hl ramphen ol 50 mg. f ur times a d y was ad led ubsequent to positive cultures f bl od and urine for *Aerobacter a ogenes*. The levarterenol was reduced t f ur ampules per liter of gl se on Augu t 5 to tw ampules on Au ust 7, and finally to one ampule on Augu t 13.

On Augu t 15 the patient w till markedly h po ten with the bl od p sure falling t zero when the int enou therapy wa t mporarily hut off. At th p nt the levarteren l w repl c d

by metaraminol 100 mg per liter of glucose this was reduced to 20 mg on August 19 and the Dicrysticin was discontinued Prednisone 5 mg four times a day and salt tablets orally were added at this time On August 20 heparin was replaced by dicoumarol and on August 29 metaraminol was discontinued and replaced by elixir of mephentermine orally four times a day Prednisone also was discontinued and replaced by hydrocortisone 5 mg and fludrocortisone acetate 0 1 mg since he continued to be hypotensive During the initial week rectal temperatures ranged between 99 6 and 100 F then averaged 98 6 F until August 30 when the rectal temperature was 97 F Subnormal temperatures then persisted during the remainder of his hospital stay On August 30 he experienced severe recurrent chest pain with radiation to both arms and the ECG taken at this time (Fig 1) suggested further subepicardial insult with possible extension of infarction However the patient did not go back into shock his blood pressure remained at 100/70 mm Hg and there were no friction rubs new murmurs or evidences of pulmonary infarction The pain subsided after meperidine was administered his progress was satisfactory and he was discharged Oct 1 1963

He had been afebrile during the hospital stay and continuously his recorded blood pressure readings were as low as 50/30 to 60/40 mm Hg through August 29 This required that the blood pressure be read every 15 minutes during the first 2 weeks and then every 30 minutes through August 29 for a total of well over 1 500 readings He was still hypotensive at the time of discharge but finally had a blood pressure of 120/70 mm Hg by Dec 1 1963

Laboratory studies included a white blood count of 73 750 per cubic millimeter on August 3 72 000 on August 5 and gradually falling to 7 950 on Aug 20 V D R L was nonreactive The blood urea nitrogen was 16 2 mg per cent Na 137 mEq per liter K 3 37 mEq per liter Cl 92 mEq per liter serum protein total 7 3 Gm per cent albumin 4 9 Gm per cent globulin 2 4 Gm per cent A/G ratio 2 011 after admission On August 3 the SGOT was 144 units with L D H 857 units The sedimentation rate was 38 mm per hour On August 4 the SGOT was 60 units and L D H 690 units and on August 5 the SGOT fell to 30 5 units with L D H 730 units On August 21 the 24 hour urine volume was 1 120 c c with ketosteroids 7 3 mg per total volume (normal 8 to 20 mg) 17 OH steroids 2 64 mg per total volume (normal 2 to 10 mg) Thorn test (on steroid) eosinophil 51 per cubic millimeter to 0 after ACTH Serum Na was 140 mEq per liter K 4 4 mEq per liter Cl 106 8 mEq per liter phosphate 2 7 mEq per liter alkaline phosphatase 6 mEq per liter creatinine 0 90 Gm per total volume 24 hour urine for five H I A A negative

The blood cultures of August 5 were positive for *Aerobacter aerogenes* with good sensitivity reaction for chloramphenicol streptomycin kanamycin polymyxin B tetracycline and Colymycin The patient was continued on Dicrysticin (penicillin 400 000 units—streptomycin 0 5 Gm) every 6 hours from August 2 through August 1 and on chloramphenicol 250 mg four times a day given orally from August 7 through August 30

The blood cultures were negative after Sept 9 1963 Total urine output was 720 c c on August 8 and from then until September 11 it averaged 420 to 660 c c The electrocardiograms (precordial lead only shown) showed evidence of anterior myocardial infarction whereas that of August 30 showed recurrent S T elevation suggestive of extension of infarction pericardial irritation or possible aneurysm The ECG on September 26 again showed normal evolution

Discussion

Many aspects of this case history are of interest (a) the onset of shock with two mechanisms myocardial infarction and gram negative bacteremia without fever chills or anginal type of pain preceding the shock reaction (b) the onset of a generalized convulsive seizure tremors of the right arm and leg and psychotic behavior with completely withdrawn personality (c) early marked leukemoid reaction and (d) the prolonged severe hypotensive state with dependence on vasopressor drugs

Shock can be initiated in different ways and is always a challenge to the clinician Severe and sustained hypotension complicating myocardial infarction is associated with a high mortality rate of 60 to 90 per cent[4-6] however this has been reduced to 40 to 50 per cent with the advent of levarterenol therapy[7] Similarly a high mortality rate of 70 per cent has been reported by Spink[8] in endotoxin shock emphasizing the high incidence of serious shock associated with infections of the urinary tract

Basically the most widely used drugs for all types of shock are the pressor agents In cardiogenic shock there is the added factor of sudden decrease in left ventricular output that results from damaged myocardium[1] When congestive failure is present digitalis will increase cardiac output and help restore circulatory dynamics Patients with shock due to gram negative bacteremia are usually treated initially with a variety of antibiotics including a tetracycline compound or chloramphenicol with oxygen and with infusions such as plasma whole blood and water with added glucose Pressor drugs are also used to maintain the systemic blood pressure and in some circumstances

glucocorticoids are administered.[9] In this case a combination of penicillin and streptomycin therapy was initiated while the results of blood cultures were being awaited, and then chloramphenicol was added as indicated by sensitivity tests. Hypothermia has been suggested in the management of bacteremic shock by some investigators,[10] and it is apparent that this patient remained fever free throughout his shock state, which factor could have contributed to his recovery. Hypothermia is thought to protect the host by altering the growth rate of the invading organisms.

Corticoids were added since it has been observed in the human subject and in the experimental animal that during prolonged hypothermia the vascular beds become increasingly less sensitive to exogenous pressor agents such as metaraminol and norepinephrine.[11] Laboratory findings in this case did not document adrenal insufficiency, which, however, may occur in some cases of shock. The fact that this patient escaped the most serious complication of endotoxin shock, namely, renal failure, suggests that levarterenol may aid the renal circulation. However, since renal failure is rather characteristic of endotoxin shock, this may also suggest that myocardial infarction played the dominant role in producing the profound hypotensive state.

Recent work emanating from Sweden suggests that increased blood viscosity may be a key element in shock, and the large amount of intravenous fluids required for the administration of levarterenol may have been useful in maintaining normal blood viscosity and hemodynamics.

Tremors, a confused state, and leukemoid reaction occurring in the same patient during shock have been mentioned in an earlier report[4]; however, they occurred in the seventh week of prolonged shock, and it was believed that the tremors represented hepatic encephalopathy due to a toxemia, prolonged shock, or metaraminol bitartrate. The leukemoid reaction was attributed to the use of metaraminol. In this case it also seems reasonable to implicate metaraminol, since leukemoid reaction is not characteristic of either gram-negative bacteremia or cardiogenic shock. The precipitous rise in the white blood count to 73,750 per cubic millimeter is of great interest. It was obviously not explained by the myocardial infarction. Included in the differential diagnosis were overwhelming sepsis (septicemia), acute leukemia, pneumonia, pneumococcal endocarditis, and, also suspect because of marked malnutrition, malignancy with metastasis. All were ruled out except the gram-negative bacteremia due to *Aerobacter aerogenes*, which characteristically produces hemolytic reactions rather than leukemoid. Thus, although the leukemoid reaction led to the additional diagnosis of bacteremia, it was more likely due to the use of metaraminol in the control of shock. This has been suggested previously in the leukemoid state.

The cause of the convulsive seizure with coarse tremors of the right arm and leg is obscure. The tremors occurred prior to the state of shock and were preceded by peculiar mental signs of withdrawal. They may well represent toxic manifestations as an early sign of bacteremia. In impending shock, compensatory vasoconstriction is reported to spare the cerebral vessels and protect the brain from anoxia.[1] Serotonin may be elevated in the early phase of shock but is not supposed to penetrate the blood-brain barrier.

Prolonged and relentless shock has been reported[4] to respond successfully to therapy. This adds a case in which vasopressor therapy was required for a total of 30 days and confirms the value of both vasopressor drugs and fluids in the treatment of combined cardiogenic and bacteremic shock.

Summary

This case history was presented because of two separate etiological factors producing shock, namely, gram-negative (*Aerobacter aerogenes*) bacteremia and myocardial infarction. In this case, shock was preceded by convulsive seizure and coarse tremors of the right arm and leg, instead of the usual occurrence late in the course of events. This was interpreted as an early toxic manifestation of impending gram-negative bacteremia with shock. Of special interest is the marked leukemoid reaction (73,750 white blood cells per cubic millimeter) with metaraminol bitartrate sus-

pect Leukemoid reaction does not occur in gram negative bacteremia which is more likely to produce hemolytic reac tions Leukemoid reaction of this degree is not characteristic of myocardial infarc tion Other causes of sepsis were ruled out The hypotensive state was profound and prolonged for a total of 30 days and responded to conventional therapy Ad renal insufficiency was suggested as a cause of prolonged hypotension but is not well documented by steroid levels reported or by the Thorn test

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Hypokalemic alkalosis with adrenal tumor

A case report Conn's syndrome or drug induced hypokalemic alkalosis

*J A H Collyns M A M B (Cantab) M R C P (Lond)**
D H G MacQuaide M D F R C P (Lond)
Northampton England

In 1954 Conn[1] described his first case of primary aldosteronism in which recovery was satisfactory after removal of a large aldosteroma. Very little in the way of additional symptomatology or biochemical findings has been added to the original description. The present case is reported because we believe it to be an example of Conn's syndrome although by no means all the criteria were satisfied. For mild cases Conn mentions newer testing procedures such as the response to potassium loading and the administration of aldosterone antagonists and compounds of the chlorothiazide type. It seems that our case was indeed mild and that the 41-day course of hydrochlorothiazide prior to hospitalization of the patient may have been an inadvertently valuable provocative test that suggested the presence of an aldosterone producing tumor.

Case report

M S a 59 year-old English housewife was first seen in February 1959. She was known to have been hypertensive for 10 years and the symptoms included giddiness, falling, ep taxes, suboccipital headache, anxiety and insomnia. Six years before she had suddenly and permanently lost the sight in the right eye. Treatment had included rauwolfia and veratrum alkaloid and phlebotomies when the systolic pressure rose above 190 mm Hg. The findings on first examination were a blood pressure of 2 0/170 mm Hg a regular ventricular rate of 90 per minute, slight cardiac enlargement with some left ventricular thrust and a short musical apical systolic murmur. The right fundus could not be seen and the left showed Grade 2 changes of arteriosclerotic retinopathy. In addition the urine contained a trace of protein. The blood urea was 33 mg per 100 ml and values for hemoglobin, leukocytes and erythrocyte sedimentation rate fell within the normal range. Treatment was started at the end of February with rauwolfia and veratrum alkaloids with hydrochlorothiazide 25 mg three times a day and potassium chloride 1 Gm three times a day.

The patient was next seen and admitted to the hospital 48 days later. She was confused, incoherent —in fact almost psychotic—and quite unable to give an account of herself. Her doctor's reason for referring her was a sudden fall in the blood pressure to levels in the range of 120/70 mm Hg. Examination revealed coupling with a ventricular rate of 88 per minute. The blood pressure was 170/ 0 mm Hg. She had very slightly diminished deep reflexes and no edema or other signs of heart failure. There was a moderate albuminuria. An electrocardiogram showed regularly recurring ventricular premature beats and long depressed RS T segment in the more normal complexes of Leads I, II, aVL and V_{4-6}. The next day the patient was cooperative, coherent *and sensible. Her main complaint was of grad*ually progressive weakness which had developed during the previous month accompanied by anorexia. Three weeks before admission to the hospital she found herself too weak to get out of bed where she remained. There were graphic descriptions of paresthesia in all four extremities and carpopedal spasms. Abdominal pain on the right side and some thirst came well down in her list of complaints. The patient denied previous significant attacks of weakness or polyuria. On examination polyuria b enuresis was

From the General Hospital Northampton England
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*Present address: Department of Internal Medicine, The University of Texas Southwestern Medical School, 5323 Harry Hines Blvd, Dallas, Texas 75235

still present with alternation of the heart detected easily on sphygmomanometry The blood pressure was 144 100/60 mm Hg and the ventricular rate was still 88 per minute Treatment at this stage consisted of a normal diet rich in potassium-containing fluids e g broth fresh orange juice and all previously prescribed drugs were discontinued

Two days after admission the blood pressure was 150/60 mm Hg the coupling had stopped and the ventricular rate was 80 per minute Urine specific gravity was 1 008 A repeat electrocardiogram on the third day after admission confirmed sinus rhythm at 79 per minute The sagging prolonged RS T segments with wide-based dome-like T waves in Leads V were characteristic of hypopotassemia K (for Q T duration) worked out according to the formula of Bazett was 0 65 (upper limit of normal 0 45) Values for plasma potassium of 1 8 mEq per liter plasma sodium 153 mEq per liter and plasma bicarbonate 37 mEq per liter were obtained the same day The urine was continuously alkaline during the patient's first week in the hospital and contained protein for the first 9 days Thereafter it was mainly neutral occasionally acid or alkaline with periodically a trace to a very slight trace of albumin After the above mentioned biochemical findings had been reported the patient was put on potassium chloride 1 Gm three times a day orally Five days after admission she mentioned a drawing up of the hand suggestive of tetany This was not repeated and she continued to improve and the blood pressure rose to the order of 200/100 mm Hg with increasing strength and confidence Deep reflexes were entirely normal The electrocardiogram 9 days after admission was that of left ventricular strain and hypertrophy A specific gravity concentration test (done 18 days after admission) showed urine specific gravity of 1 018 (after an 18-hour thirst) There was a mild pyrexia up to 99 6°F for 9 days after admission With the exception of the plasma potassium which was never above 3 4 mEq per liter normal values were obtained preoperatively for plasma chlorides bicarbonate and sodium Estimation of urinary aldosterone 30 days after admission was 2 45 µg per day (average of 2 days) This estimation was carried out at St Thomas Hospital London and the normal range there at the time was 3 to 8 µg per day Other investigations which were either normal or noncontributory included blood urea excretion pyelogram retroperitoneal pneumogram hemoglobin leukocytes blood film etc

Operative procedure Thirty three days after admission the adrenals were explored the patient being at the time under cortisone and hydrocortisone cover with potassium chloride by mouth as advocated by Thorn The right adrenal gland was deemed to be normal but the left adrenal gland was judged to be about twice normal size with some surrounding reaction After removal it was found to contain a tumor about 1 cm in diameter (Figs 1 3) The pathologic report on the specimen is as follows

MACROSCOPIC The suprarenal gland was received fixed and measured 4 0 by 2 7 by 0 9 cm There was a slightly pedunculated yellow tumor measuring 1.3 by 1.3 by 1 0 cm which projected from the upper

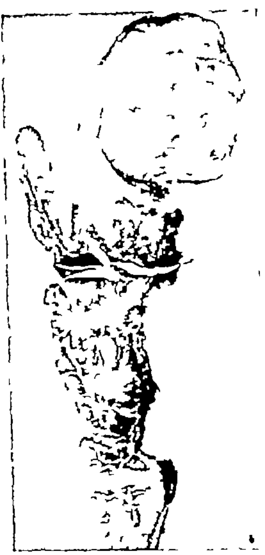


Fig 1 Left suprarenal gland with prominent cortical adenoma (hematoxylin and eosin ×4)

surface at one end of the gland On cut section the tumor was golden yellow and homogeneous in appearance

MICROSCOPIC The tumor was a suprarenal cortical adenoma composed of well-differentiated lipoid rich cells with small generally inconspicuous nuclei At the periphery of the tumor some cells which contained less lipoid were present and in this area some cells had rather large hyperchromatic nuclei There was nothing to suggest malignancy The adenoma appeared to have arisen from the zona glomerulosa Many of the smaller blood vessels particularly in the immediate vicinity of the adenoma showed a good deal of hyaline arteriosclerosis amounting to almost complete vascular obliteration in a few instances The remaining suprarenal tissue showed a normal medulla the cortex being perhaps slightly hyperplastic with a slightly reduced amount of cortical lipoid

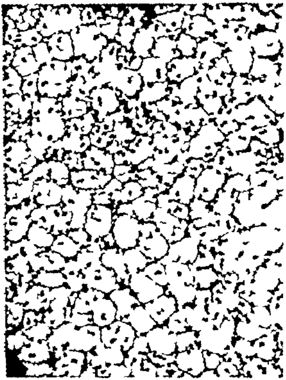


Fig. 2. Higher power view of tumor (hematoxylin and eosin X1 ?)

Postoperative course. The lowest recorded blood pressure in the immediate postoperative phase was 150/90 mm. Hg. Thereafter in the hospital and in the follow-up, hypertension of the order of 200/100 mm. Hg were encountered. The postoperative course gave no cause for alarm objectively even when cortisone was discontinued and the striking feature was the *remarkable feeling of well being and strength* immediately after the operation which has continued in marked contrast to the preoperative weakness. The level of plasma potassium was first found within the normal range at 4.3 mEq. per liter on the first day after the operation. Three months later at follow-up interview she had just returned from a holiday *free from the episodes* which had previously marred all her activities. The blood pressure was 200/100 mm. Hg and she was able to do her usual household *jobs*. The patient elaborated protein-free urine with a specific gravity of 1.0?? after an 18 hour thirst. Blood urea was 44 mg. per 100 ml. Plasma potassium was 4.7 mEq. per liter, plasma sodium 150 mEq. per liter, plasma chlorides 106 mEq. per liter, and plasma bicarbonate 2? mEq. per liter.

Discussion

Painless myocardial infarction was at first considered as a possible explanation for the state of collapse and arterial hypotension. The ECG findings did not bear this out and we resisted this diagnosis despite an initially raised erythrocyte sedimentation rate and fever for 9 days. Diagnosis on admission was made more difficult by the almost negligible history due to the patient's confused and incoherent state, a feature not greatly emphasized in the literature on Conn's syndrome or low potassium states. Fortunately the next day the patient gave a most helpful anamnesis. Conn describes the symptomatology under 5 headings: (1) muscular weakness, (2) muscular tetanic manifestations, (3) polydypsia and polyuria, (4) severe headache, and (5) paresthesias. Our patient had all these complaints except the polyuria and polydypsia. In regard to the physical findings, Conn mentions (1) hypertension, (2) Chvostek and Trousseau signs, (3) cardiac enlargement, and (4) absence of edema.

Our patient, despite a long history of hypertension, was normotensive (blood pressure 120/70 mm. Hg) on admission to the ward and regained her more usual blood pressure, 200/96 mm. *Hg*, only after 14 days of treatment with potassium supplements orally. This blood pressure may have simply been an exemplary response



Fig. 3. Still higher power view (hematoxylin and eosin X600).

to therapy but Rauwiloid Veriloid and hydrochlorothiazide had all been discontinued 1 week before admission to the hospital without any effect on the blood pressure which remained in the range of 145/65 mm Hg Alternatively the lower systemic blood pressure may have been an expression of severe cardiac muscle weakness Necrosis and hyalinization of cardiac muscle[1] are observed in the more severe grades of potassium depletion and these may have played their part in lowering the tension We were not able to elicit signs of tetany but cardiac enlargement was present and edema absent Under laboratory findings Conn[2] lists 12 items Of these our case demonstrated 6 i e hypopotassemia hypernatremia alkalosis intermittent mild albuminuria slightly decreased renal function as demonstrated by poor concentrating power (decreased tubular reabsorption of water) and ECG changes typical of hypopotassemia Goldberger[3] has noted that regularly recurring ventricular premature beats as in our patient s first record may be a feature of the electrocardiogram in hypopotassemia even in patients who have never received any digitalis We were unable to demonstrate an increase in the urinary level of aldosterone (average of two samples of urine) However Conn has stated that in primary aldosteronism excessive amounts of aldosterone may not be detectable in the urine on all days and that multiple determinations may be required to demonstrate the presence of hyperaldosteronemia Conn s experience[2] suggests that if all the classic findings are insisted upon only 30 per cent of the cases will be diagnosed He mentions cured patients with proved primary aldosteronism who were asymptomatic preoperatively but who were known to be hypertensive Only routine testing of serum potassium levels in hypertensive persons leads to case detection The renal lesion in the case here presented was presumably what has been termed kaliopenic nephropathy This is a vacuolar lesion mainly in the proximal tubules Much of the tubular lesion is reversible by treatment which raises the level of serum potassium The renal concentrating ability of our patient improved after surgery Such patients in addition have a high incidence of renal arteriolosclerosis and pyelonephritis

Role of hydrochlorothiazide It was postulated that the adrenal cortical adenoma might have been without endocrine significance and that possibly hydrochlorothiazide by mouth 25 mg three times a day for 41 days prior to hospitalization was alone responsible for the profound biochemical alterations found on admission Potassium chloride supplements 1 Gm three times a day were given with the hyrochlorothiazide and continued up until the time of hospital admission The hydrochlorothiazide itself was discontinued 1 week before the patient came into the hospital and 9 days before her plasma ionic pattern was studied Many electrolyte-depletion syndromes have been described in association with the prolonged and aggressive exhibition of powerful diuretic drugs in particular mercurials Thus Harrison and Resnick[4] list the low salt syndrome the potassium-deficiency syndrome the salt-dilution syndrome and the syndrome of hypochloremic alkalosis In the latter the body stores of potassium are depleted although the level of serum potassium may be normal The plasma electrolyte pattern in hypochloremic alkalosis most closely resembles that found in our patient except that the serum sodium remains at or near to normal levels The original plasma chloride in our case was 88 mEq per liter and the plasma sodium of course was characteristically raised to 153 mEq per liter These electrolyte-depletion syndromes are produced in patients who are or have been edematous usually in heart failure presumably often with secondary hyperaldosteronism and who have in general received diuretic drugs for a period considerably longer than the 6 weeks seen here When hydrochlorothiazide is used for its antihypertensive action in cases of nonedematous hypertension with or without Rauwiloid and veratrum alkaloids the most frequent change in blood chemistry is a reduction in the serum potassium by more than 0 4 mEq per liter in about 40 per cent of the cases and to 3 5 mEq per liter (the lower range of normal) in about 20 per cent of the cases[7] A decrease in serum sodium of greater than 8 mEq per liter accompanies

by a reduction in serum chloride also is uncommon being found in 8 per cent of the cases and a rise in blood urea nitrogen by 10 to 14 mg per 100 ml also is recorded in 6 per cent of the cases These changes in urea nitrogen and serum electrolytes reverted to control values after withdrawal of the drug and were recorded in patients with restricted intake of sodium and without the benefit of potassium supplements by mouth It is stated that these changes in blood chemistry usually were not clinically detectable It was the striking clinical manifestations and in particular the hypernatremia that suggested to us that the syndrome could not be accounted for solely by the drugs which the patient had been receiving

Summary and conclusions

1 A case of hypokalemic alkalosis associated with an adrenal tumor is described

2 Only a percentage of the clinical and laboratory features described by Conn in cases of primary aldosteronism were detected in this case however we believe that this may well have been a true case of Conn s syndrome

3 Hydrochlorothiazide therapy is considered to have acted as a provocative agent and to have made an early diagnosis possible

Thanks are due to Mr R O Lee who performed the surgery Dr R A Sladden for the pathological report Professor R G Prunty and Dr M A Floyer for much help and encouragement to CIBA Ltd Basle Switzerland for help with the bibliography and to Dr Margaret B Carter for referring the case to us and providing the opportunity for study of an as yet uncommonly recognized hypertensive syndrome

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Clinical pathologic conference

Cecil A. Krakower, M.D.
Nicholas J. Cotsonas, M.D.
Chicago, Ill.

Clinical abstract

History. A 43-year-old white married man, a receiving clerk, was first seen in the Medical Clinic of the Research and Educational Hospitals 3.5 months prior to his death. He had been in excellent health until about 6 or 7 months earlier, when he noted dyspnea on climbing three flights of stairs. He was more fatigued than usual but continued to work. One month earlier, ankle edema developed. He had no palpitations, chest pain, orthopnea, paroxysmal nocturnal dyspnea, cough, or respiratory infections. He had always preferred warm weather. His appetite was good and there was no change in weight or bowel habits. A friend had told him that he looked yellowish, but there were no changes in the color of stool or urine. No itching was noted. Nocturia was present once, diuria four to five times. There were no chills or fever. The patient had smoked one package of cigarettes daily for 15 years. He drank 3 to 4 quarts of beer over weekends but no whiskey. He had had pneumonia in childhood and a left inguinal herniorrhaphy at the age of 37. There was no history of rheumatic fever, hypertension, heart murmurs, or respiratory diseases. He had no allergies or any exposure to dusts or chemicals. During an Army examination 20 years earlier and a preherniorrhaphy checkup, no cardiac abnormalities were noted or mentioned to the patient. The patient's father was well at 70. His mother, at age 67, his maternal grandfather, and 7 uncles and aunts had all died of heart attacks or enlarged hearts in their forties or fifties. There were no other diseases in the family.

Physical examination in the Clinic during the initial visit revealed no distress. Clubbing was noted but, according to the patient, this had been present all through life. The color was good. There was neither cyanosis nor venous distention. There was no definite cardiac enlargement. S_2 was widely split, the splitting increased with expiration and decreased with inspiration. A Grade 4/6 ejection murmur was heard over the entire chest anteriorly and on the left side posteriorly, as well as in the axilla and over the neck. The maximal intensity of the murmur was in the third left intercostal space. Otherwise there were no abnormal physical findings.

The urine contained one-plus protein, no sugar, and a few hyaline casts. The hematocrit was 33.5 per cent. The white blood cell count was 8,800 with a normal differential. The blood serology and chemistries were normal. Four views of the chest after barium swallow revealed elongation and widening of the thoracic aorta, possible right ventricular prominence, and an old pleuritic reaction at the left base. The ECG showed right ventricular hypertrophy and ST-T wave changes consistent with digitalis effect (Fig. 1). Since no definite diagnosis could be established, the patient was scheduled for cardiac catheterization. Meanwhile he was maintained on digitoxin 1.5 mg., chlorothiazide 500 mg., potassium chloride 0.9 Gm., and ferrous sulfate 0.9 Gm. daily, and was doing well. Two to 3 weeks prior to admission the dyspnea increased. On the evening prior to admission the patient had nausea and vomiting, and during the night he was awakened with sudden dyspnea. He became cyanotic and was admitted to the Research and Educational Hospitals in severe respiratory distress. There was no history of chest pain or syncope.

Physical examination on admission revealed an acutely ill cyanotic man. The blood pressure was 110/80 mm. Hg, the pulse was 176 and regular, and the respirations were 36. The temperature was 100° (R). The neck veins were distended up to the angle of the jaw at 40 to 60 degrees elevation. The chest was clear on percussion, but there were rales at the left base anteriorly and scattered rales at both bases posteriorly. The point of maximum impulse was not felt. There were no bulges, left parasternal lift, or left ventricular heave. S_1 was maximal at the apex but not split. S_2 was widely and rather constantly split, maximal at the second and third intercostal spaces. A Grade 3/6 ejection type of systolic murmur was best heard in the third left intercostal space. There was neither an opening snap nor a diastolic murmur. One observer heard a pulmonary systolic click. The edge of the liver was down 2 to 3 fingerbreadths. Otherwise there were no abnormal findings in the abdomen. There was moderate clubbing but no ankle edema. The remainder of the physical examination was negative. The hematocrit was 47 per cent and the hemo-

From the University of Illinois Research and Educational Hospitals, Chicago, Ill.
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Address: Department of Pathology, University of Illinois College of Medicine, [illegible] West Polk St., Chicago, Ill.

globin was 13.2 Gm. The white blood count was 19,100 with 10 per cent stab, 76 per cent segmented neutrophils, 11 per cent lymphocytes, and 3 per cent monocytes. The electrolytes were normal. No specimen of urine was obtained. A portable chest film suggested a pneumonic infiltrate in the left lower lobe and also possible bilateral pleural effusions. The ECG showed QS waves in Leads I, aVL and V1-V4 with no ST-T changes suggestive of acute myocardial infarction. The respiratory distress increased 5 hours after admission. The patient became frankly cyanotic and disoriented. The blood pressure was unobtainable but the skin was not clammy. He was treated with vasopressor, 5 million units of penicillin intravenously, and intermittent positive pressure with oxygen. The cyanosis deepened however. Finally, heart action ceased and did not respond to closed-chest cardiac massage. Death occurred 8 hours after admission.

Discussion

DR. COTSONAS: The important points in the history of this patient are these: (1) Nine members on the maternal side of his family had died of heart attacks or enlarged hearts in their forties or fifties. (2) No cardiac abnormality was commented upon when he was examined for military service at age 23 or when he had his hernia repaired at age 32. (3) When clubbing was called to his attention, he stated that it had been present all of his life.

When he developed symptoms, these were suggestive of congestive heart failure with dyspnea on exertion, ankle edema, and easy fatigability. When he was seen in the Medical Clinics 3½ months before his death, the important findings were: (1) clubbing, (2) absence of cyanosis, (3) no definite cardiac enlargement or evidences of congestive heart failure, (4) widely split S2 (and we are told that the splitting increased with expiration and decreased with inspiration, which suggests that he was examined by someone of some sophistication), (5) a Grade 4-6 ejection murmur over the entire chest anteriorly and on the left side posteriorly, also in the axilla and over the neck (the maximal intensity of the murmur was in the third left intercostal space), (6) roentgen evidence of elongation and widening of the thoracic aorta, possible right ventricular prominence and an old pleuritic reaction at the left base, and (7) electrocardiographic evidence of right ventricular hypertrophy and changes consistent with digitalis effect.

The first question is whether the patient had congenital or acquired heart disease.

In favor of congenital heart disease are the family history and the presence of clubbing. The latter suggests a small right-to-left shunt which produced some degree of arterial oxygen unsaturation, and which, because of a larger left-to-right shunt, was insufficient to produce clinical cyanosis.

Let me consider first those forms of congenital heart disease which permit the body to receive an adequate supply of oxygen, and which are not characterized by cyanosis until late in the course, if at all. In addition, let me specify those acyanotic forms of congenital heart disease in which the electrical preponderance is on the right side: (1) pure pulmonary stenosis, (2) ventricular septal defect in which the electrical preponderance may be on either side, (3) anomalous venous return, and (4) atrial septal defect. I would like to dismiss pure pulmonary stenosis because the sound of pulmonary closure is usually diminished or absent, and there usually is a thrill as well as a murmur. Patients with pure pulmonary stenosis are not usually cyanotic except terminally with failure. I would also like to dismiss ventricular septal defect because the murmur is not so likely to be missed earlier in life.

Anomalous pulmonary venous return into the right atrium or its tributaries is found at all ages and even incidentally. Unless complicated by an associated defect, it is compatible with long life. It is frequently associated with a patent foramen ovale or an atrial septal defect, but is rarely associated with pulmonary stenosis or other malformations. From a physiologic point of view, anomalous pulmonary venous drainage is similar to an atrial septal defect, producing a large left-to-right shunt with recirculation of a significant amount of blood through the lungs. Without a complicating lesion or alterations in the pulmonary vessels, the degree of pulmonary hypertension is not great. Murmurs are usually absent, but when present there is a systolic murmur of variable intensity in the second and third intercostal spaces on the left, and it may be accompanied by a thrill. In fact, in one series two thirds of the patients without pulmonary stenosis had such a murmur and

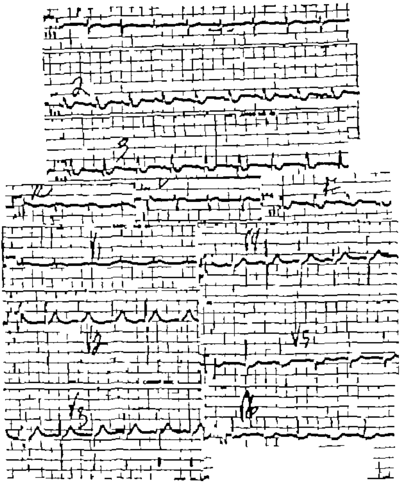


Fig. 1. Electrocardiogram. Rate 93, rhythm sinus. P-R duration 0.15 sec. QRS duration 0.08 sec. Small q in Leads II, III, aVF, and V. Small upright QRS in Lead V_1. Prominent S in Lead I. R is greater than S in Lead V. Depressed S-T in Leads II, III, aVF, and V. Slightly elevated S-T in Lead aV. Inverted T in Leads II, III, and aV. Terminally inverted T in Lead aVL. Diphasic T in Leads V.

thrill. The ECG may be normal or show the changes described in this patient. On the x-ray film, the right atrial silhouette is prominent because of increased blood flow. There are a number of suggestive x-ray findings, but the one which I wish to stress is that when the pulmonary veins enter the left innominate vein, there is usually a persistent left superior vena cava at the left hilum and superior mediastinum, producing a picture which has been mistaken for mediastinal and hilar adenopathy or an aneurysm of the great vessels. Because of the increased flow and volume, if there is a patent foramen ovale or an atrial septal defect, a portion of the oxygenated blood mixed with the systemic venous blood may be shunted through the opening and produce some unsaturation or even cyanosis. On auscultation and by phonocardiography, the interval between the two components of the second sound may show greater variation than that expected in an atrial septal defect with a left-to-right shunt of comparable size. However, it has been reported that 20 per cent of the patients with atrial septal defects have paradoxical movement of the aortic valve closure.

So I conclude that I cannot dismiss anomalous pulmonary venous drainage since I find many things attractive

it. If he had it, I suspect that it was in association with a patent foramen ovale or an atrial septal defect.

There is nothing incompatible in this case with atrial septal defect except that the x-ray films suggest a dilated, unfolded aorta. I would, however, have to invoke some mechanism for the pulmonary hypertension. The usual factors, such as recurrent infections, pulmonary emboli, etc., are missing. The coexistence of pulmonary stenosis may cause a right-to-left shunt through the patent foramen ovale.

I would like to turn now to a consideration of those cardiac states which relate to the description of the second sound. The description suggests paradoxical splitting of the second sound. Paradoxical splitting occurs when the pulmonary valve closes before the aortic valve. This change in the normal order of closing is recognized by narrowing or closure of the split during inspiration. Paradoxical splitting occurs in conditions which prolong left ventricular ejection time, such as aortic stenosis, left bundle branch block, patent ductus arteriosus with left-to-right shunt, in some cases of systemic hypertension. From the information available, I can dismiss left bundle branch block and hypertension. Because of the electrical preponderance on the right, I should be able to dismiss aortic stenosis. The absence of a diastolic component makes patent ductus arteriosus unlikely.

What conditions would I have to consider if there were wide splitting of the second sound, but the splitting was increased on inspiration. I know this is not what the protocol says, but it is possible that the observer was correct in noting that there was a wide split of the second sound, but what he really was noting in addition was that there was respiratory variation in the splitting. The conditions are: (1) pulmonary stenosis (in which it is reported that the width in expiration is related to the severity), (2) moderate to severe mitral insufficiency, (3) right bundle branch block, (4) tetralogy of Fallot (in which the pulmonary closure may be inaudible but is seen phonocardiographically), and (5) defect of the ventricular septum. I can dismiss right bundle branch block because it is not present and tetralogy of Fallot because there was no cyanosis. I think that mitral insufficiency is unlikely because of the electrical preponderance on the right and the fact that the murmur had ejection qualities.

It is interesting that pulmonary stenosis and ventricular septal defects crop up again. Let us suppose that the observer's only valid observation was wide splitting of the second sound. This is characteristic of atrial septal defect and is sometimes present in defects of the ventricular septum. I am therefore about where I started, with the same four possible congenital cardiac anomalies as were first considered.

Let us suppose that he had acquired heart disease. The striking findings are elongation and widening of the thoracic aorta—suggesting ectasia or dissection and progressive right ventricular hypertrophy. It is at this stage that a review of the x-ray films may be helpful in deciding between congenital and acquired heart disease.

DR. GREENFIELD: The first set of films is an examination of the chest with barium in the esophagus approximately 3 months prior to the date of the last portable chest film. The heart shadow is not enlarged on anteroposterior view. There is fullness of the retrosternal space which is consistent with the electrocardiographic changes of right ventricular hypertrophy. There is some prominence of the aorta. The pulmonary artery is also slightly prominent. The pulmonary vasculature peripherally, however, may be slightly decreased (Fig. 2 *a* and *b*).

The portable chest film was taken prior to death. The heart shadow cannot be evaluated. There is increased prominence of the pulmonary artery. The peripheral pulmonary vasculature is not increased. There is infiltration in the left lung base. There is evidence for bilateral pleural effusion. In addition, there is a suggestion of a rounded density in the retrocardiac region blending with the shadow of the descending aorta which was not previously present. This finding cannot be completely evaluated on a portable film (Fig. 2 *c*).

DR. COTSONAS: The films as projected by the roentgenologist can be summarized as follows. We infer a decreased pulmonary blood flow because the pulmonary vascular markings are definitely reduced. There is

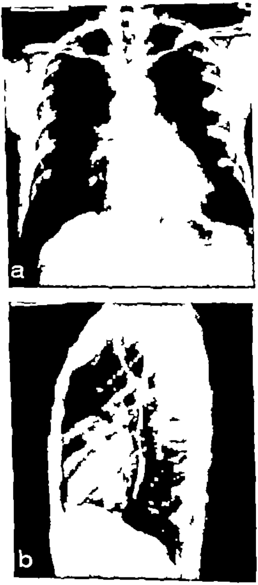


Fig. X ray of film of the chest a Anteroposterior view b Lateral view with barium in esophagus There is fullness of the retrosternal space consistent with right sided ventricular hypertrophy There is prominence of the aorta

however prominence of the main pulmonary artery The combination of these two findings strongly suggests pulmonary stenosis In keeping with this there is a large right ventricle There is also prominence of the ascending aorta The roentgenologist and I differ on this point I believe that there is moderate enlargement of the ascending aorta and he believes that it is only slight

On these grounds I would dismiss acquired heart disease and conclude that the patient had pulmonary valvular stenosis with coexisting undiagnosed congenital defects

DR. KRAKOWER The pertinent findings at postmortem examination relate to the mediastinum and heart There was an anterior mediastinal tumor which encased the ascending aorta anteriorly and laterally and infiltrated the concave aspect of the transverse and descending arch The tumor was firm gray white reaching a thickness of 2.0 cm in places It infiltrated the medial portion of the upper lobe of the right lung over an area 4.0 by 3.0 cm and the medial middle sector of the upper lobe of the left lung Both these portions of lung were drawn medially so as to be obscured by the overlying sternum In addition tumor infiltrated the parietal and visceral pericardium of the anterior upper third of the heart Despite this there was no excess of fluid in the remaining nonadherent pericardial sac although there were areas of epicardial thickening and hemorrhage The heart weighed 450 grams but this included some of the mediastinal tumor The intrapericardial portion of the superior vena cava was encased by tumor On its intimal sur

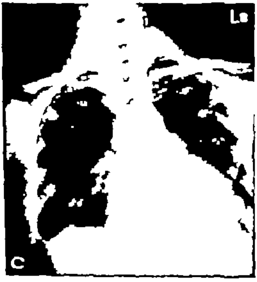


Fig. 2 c Portable chest x ray film which shows positive retrocardiac density blending with the shadow of the descending aorta

tinct narrowing of the circumference of the infundibulum In the region of the pulmonary valve the circumference was reduced to some 3 5 cm (normal 8 5 cm) The orifice was clearly stenotic One could not be certain whether there was any degree of insufficiency however The distal pulmonary artery and its branches were not remarkable There were no thrombi or emboli The left atrium was within normal limits and the pulmonary veins entered normally into it These veins were not constricted The mitral valve measured 9 5 cm in circumference (normal 10 cm) Its leaflets were normal The left ventricle was rather small There was some endocardial opacity in the superior third or half of the outflow tract The inflow tract measured 8 0 cm in length the outflow tract 9 5 cm The myocardium of the left ventricle measured 1 0 cm in thickness at its base at the level both of the inflow and the outflow tracts The aortic valve measured 6 4 cm in circumference (normal 7 5 cm) There were some atheromatous changes in the walls of the aortic sinuses and some in the aorta above the free margins of the cusps The ascending aorta measured 5 7 cm in circumference and was free of atheroma There was some atherosclerosis of the transverse and descending arch The rest of the thoracic aorta measuring about 5 2 cm in circumference showed little atherosclerosis as did the abdominal portion The right coronary artery was encased by tumor in its first 1 0 cm and consequently somewhat narrowed but patent Likewise the left anterior descending coronary artery was encroached upon by tumor in its first 2 or 3 cm The lumen here was markedly narrowed by concentric atheromatous thickening The left circumflex coronary was short There were few atheromatous plaques in the remainder of the dominant right coronary artery and in the remainder of the left anterior descending artery The myocardium predominantly of the right ventricle had a mottled and striped yellowish and gray red appearance There were no gross infarcts Microscopically there was fatty metamorphosis of the muscle fibers There were also areas of interstitial edema with some polymorphonuclear and round cell infiltration and some increase in fibrillar connective tissue The epi

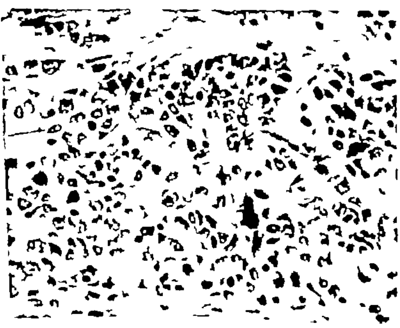


Fig 4 Microscopic appearance of the tumor There are small lymphoid cells blending with large epithelial like elements The latter tend to form Hassall like corpuscles

cardium and endocardium in areas away from the tumor also showed such inflammatory changes

Aside from the areas of tumor infiltration already described there was extension of tumor along the major structures of the upper lobe of the left lung radiating from the infiltrate bound medial portion There were 3 small pleural metastases on the left and a number of similar ones scattered over the pleura of the right lung There were no pleural adhesions or effusions There was a discrete metastatic nodule in one left bronchial lymph node The tracheobronchial lymph nodes were otherwise free of tumor as were all subdiaphragmatic organs and structures

There were marked changes of passive congestion in the abdominal viscera associated with central necrosis in the liver Despite this ascites and peripheral edema were absent There were no lymphoid infiltrates in striated muscle such as are seen in myasthenia gravis

Microscopically the tumor was made up of small round and short spindle shaped cells The latter in places assumed an epithelial appearance attempting to form Hassall like corpuscles in instances (Fig 4) There were extensive areas of necrosis and other areas of rather marked fibrosis with or without hyalinization The structure of the tumor was in keeping with that of a malignant thymoma

The physicians who studied this patient in the clinic thought that he had an isolated pulmonary stenosis A cardiac consultant who saw him terminally when he was deeply cyanosed suggested a diagnosis of tetralogy of Fallot complicated by pulmonary embolism The difficulty in arriving at a diagnosis in this case lay in the unique behavior of this mediastinal tumor Instead of expanding anteroposteriorly and laterally it maintained a fairly strict midline position about the ascending aorta with ultimate involvement of the pulmonary valve and pulmonary infundibulum narrowing both Consequently the usual x ray findings for a mediastinal tumor were lacking Even in the terminal x ray film albeit a portable one it was questionable whether there was a mediastinal mass The issue was further confused by distortion and enlargement of the aortic shadow radiographically in the face of an acceptable pulmonary stenosis clinically Furthermore the failure of the tumor to produce significant compression of the main intrathoracic venous channels or the tracheobronchial tree deprived the clinician of signs and symptoms which raise a suspicion of such a lesion Neither was the physician s task made any easier by the fact that although the tumor was of the nature of a malignant thymoma there was no accompanying myasthenia gravis

The cause for the rapidly progressive dyspnea and the marked cyanosis terminally is not entirely clear It was less likely to have a pulmonary basis since there were mild pulmonary edema minimal congestion and little in the way of pneumonia It was more likely to have a cardiac basis with acute right sided failure since there were significant fatty changes in the myocardium of the right ventricle with interstitial inflammation Both narrowing of the coronary arteries and tumor infiltration of the epicardium and myocardium may have played a role in producing these myocardial changes

Diagnosis Malignant thymoma with involvement of pulmonary valve and infundibulum leading to stenosis

Fundamentals of clinical cardiology

Restrictive cardiac disease Pericarditis and the myocardiopathies

*Ralph Shabetai, M.D.**
Noble O. Fowler, M.D.
John C. Fenton, M.D.
Cincinnati, Ohio

An incorrect diagnosis of valvular or myocardial disease may be made when constrictive pericarditis or pericardial effusion are overlooked as causes of edema with persistent elevation of venous pressure. Recently, there have been several reports of almost the reverse situation. It has been demonstrated that either idiopathic or specific myocardiopathy may simulate both clinically and hemodynamically constrictive pericarditis or pericardial effusion. This paper presents a brief review of the pathologic physiology and distinctive clinical features of pericarditis and restrictive myocardial disease.

The volume of liquid required to produce cardiac tamponade depends upon the state of the parietal pericardium, the size of the pericardial sac, and the rate of accumulation of liquid. The normal pericardium is compliant, but the pericardium which is thickened or acutely stretched has very little compliance. This rigidity is responsible for the sequence of rapidly falling cardiac output and systemic arterial pressure with rapidly rising venous pressure leading to circulatory arrest, which may occur when relatively small volumes of liquid accumulate rapidly in the pericardial space. Pressure-volume curves have been constructed for the pericardial sac of man and animals.[1] Twenty or more milliliters of liquid may enter the pericardial space without detectable change in pericardial pressure. Additional amounts of liquid raise the intrapericardial pressure exceedingly gradually and then slightly more steeply until after 100 to 300 ml., depending on the size of the subject or animal, a break occurs in the curve. Beyond this point, the addition of 5 or 10 ml. of liquid causes a very steep rise in pressure. In dogs with severe cardiac tamponade the addition of a further 10 ml. of liquid in the pericardial sac may cause the disappearance of detectable flow and pressure pulses in the aorta. In one study, when the intrapericardial pressure was raised from its normal subatmospheric level to 20 mm. Hg, circulation ceased with equilibration of pressures in the pericardium, the left atrium, the right atrium, the aorta, and the pulmonary artery.[2] In acute cardiac tamponade in man, removal of 10 to 30 ml. of blood or fluid from the pericardium may restore the patient from a moribund pulseless state to a condition of clinical comfort with easily recorded pulses and blood pressure.

Chronic constrictive pericarditis and slowly developing pericardial effusions usu

From the Cardiac Research Laboratory, Cincinnati General Hospital, and the Division of Cardiology, Department of Medicine, University of Cincinnati, Cincinnati, Ohio.
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*Address: Cardiac Research Laboratory, Cincinnati General Hospital, Cincinnati, Ohio.

ally do not cause the resting cardiac output to fall much below normal although the response of cardiac output to exercise is diminished[8] Very large volumes of liquid amounting to a liter or more may accumulate slowly in the pericardial sac without causing cardiac compression

Venous pressure and venous return

When intrapericardial pressure is raised by liquid under tension in the sac left and right atrial pressures and ventricular diastolic pressures are elevated[3,4] Left atrial pressure remains 1 or 2 mm Hg higher than right atrial pressure[3,4,6] Pulmonary venous and systemic venous pressures rise to exceed pericardial pressure in order to maintain the circulation

In the dog atrial and ventricular diastolic pressures at first rise in parallel with intrapericardial pressure as liquid is forced into the pericardial sac With severe compression intrapericardial pressure rises more than the intracardiac pressures so that pericardial pressure exceeds the atrial and ventricular diastolic pressures[6,7] Diastolic subatmospheric pressure in the cardiac chambers suggests that the heart possesses the potential to fill by suction under these circumstances[6,7] Whether it actually does so has not yet been determined by measurement of flow in the venae cavae and pulmonary veins under these circumstances It is postulated that the development of negative transmural ventricular diastolic pressure may be the result of abnormal restriction of ventricular diastolic volume by the pericardium[7] When intrapericardial pressure is continuously increased transmural diastolic pressure in the left ventricle becomes subatmospheric before that in the right ventricle However the right ventricular pressure pulse is more profoundly altered than is the left because it is necessary to raise the intrapericardial pressure very close to right ventricular systolic pressure before right ventricular diastolic pressure becomes negative[7] Right ventricular systole may be very brief in these circumstances[7] and the right ventricle in acute cardiac tamponade does not generate a normal pressure head for perfusion of the pulmonary circulation[8]

It is well known that venous return through the venae cavae is normally substantially increased during inspiration[9] It has recently been shown in our laboratory that during acute cardiac tamponade in dogs the flow of blood to the right heart through the venae cavae is increased during inspiration in much the same manner and degree as normally[10,11] Inspiratory increase in vena caval flow in acute cardiac tamponade may be an important mechanism in maintaining the circulation because the respiratory pump helps to fill the compressed right ventricle It will be shown later that the phenomenon of inspiratory increase in vena caval flow is essential for the development of pulsus paradoxus in acute cardiac compression We have been unable to find published records of pulmonary venous flow in cardiac tamponade but there is much indirect evidence that it diminishes during inspiration[11,14]

Systemic blood pressure In experimentally produced cardiac tamponade arterial pressure falls as the severity of cardiac compression increases[1,4] Pulsus paradoxus may be defined as a greater than normal inspiratory fall in arterial pressure In acute experiments pericardial pressures raised by 10 mm Hg are associated with obvious pulsus paradoxus As intrapericardial pressure is further increased from this value to 20 mm Hg the arterial pressure falls and when systolic pressure is reduced to 50 mm Hg or less little or no pulsus paradoxus remains[4]

In our laboratory studies of dogs with acute cardiac tamponade have shown that pulsus paradoxus reflects an abnormal inspiratory fall in left ventricular stroke output This fall is in part the result of an inspiratory increase in right heart volume compressing the left heart because the pericardium is unyielding[10,11,14,15] Inspiration increased systemic venous return and right heart output in our animals with acute cardiac tamponade to approximately the same extent as in the controls When respiratory variation in right heart filling was prevented by diverting the systemic venous return and pumping it at constant rate into the right atrium acute cardiac tamponade of whatever severity consistently failed to cause pulsus paradoxus[10,11] In our laboratory we have

found that pericardial effusion does not produce pulsus paradoxus when there is incompetence of the aortic valve. Retrograde filling of the left ventricle from the aorta hides the inspiratory decrease in filling from the pulmonary veins.

When the inspiratory increase in right heart filling was simulated by the sudden injection of a volume of blood into the right atrium, the results differed strikingly between the control and the tamponade animals. In controls the additional volume was immediately reflected by a temporary rise in pulmonary arterial pressure, followed two or three beats later by a temporary rise in aortic pressure. In dogs with acute cardiac tamponade the additional volume caused a similar rise in pulmonary arterial pressure but was accompanied by a simultaneous fall in aortic pressure and an increase in pericardial pressure, after which the aortic pressure rose as it had in the controls.[22]

In normal human subjects and in dogs, systemic venous return[9] and right ventricular dimensions[17] and output are greatly decreased during expiration. Therefore, aortic pressure and stroke flow[18] and left ventricular dimensions[17] begin to decline in the quiet phase of respiration and the fall continues into the succeeding inspiration.[22] The respiratory changes in systemic blood flow are less than those in the pulmonary circulation[illegible] because of storage and damping in the capacitance vessels of the lungs[1] and in the heart.[9] Transmission of falling intrathoracic pressure to the aorta further lowers aortic pressure during inspiration.[24] The abnormal inspiratory fall in aortic pressure with cardiac tamponade which constitutes pulsus paradoxus results from a further decline in left ventricular output as the inspiratory increase in right heart filling raises intrapericardial pressure.

Clinical hemodynamic findings. When motion of the heart is restricted, the fundamental alteration in hemodynamics is impaired diastolic filling of the ventricles, especially during circumstances that normally require increased cardiac output. In early diastole the ventricles fill rapidly at low pressure, but later filling is slow and the diastolic pressure is at abnormally high levels. This abnormal pattern of filling gives rise to the characteristic clinical signs and to the findings at cardiac catheterization.

Cardiac catheterization is very helpful in the diagnosis of cardiac restriction but is less helpful in determining the cause of the restriction. In general, the stroke volume is higher and the left atrial pressure is lower in pericardial compression than in myocardial restriction.[5] In all forms of restriction the equal height of the *a* and *c-v* waves, the steep *x* and *y* descents, and the lack of respiratory variation impart a W or an M pattern to the venous and atrial pressure pulses.[19] Sawyer and associates made a detailed study of the hemodynamic findings in 6 patients with constrictive pericarditis. They found that the pulmonary capillary pressure (wedge pressure) was elevated in all instances and that the systemic venous pressure was elevated and was approximately equal to the pulmonary capillary pressure. They concluded that pulmonary venous congestion in constrictive pericarditis resulted from involvement of the left ventricle, but that it was ameliorated by decreased ejection from the right ventricle. The right and left ventricular pressure pulses displayed an early diastolic pressure dip which was rapidly inscribed and which often reached subatmospheric values. The diastolic dip corresponds in time with the rapid *y* descent and deep trough of the venous pressure, and a pericardial knock sound is recorded simultaneously with its upstroke. The sharp collapse of early diastolic pressure is followed by a plateau of elevated pressure which characteristically attains a value which is one third or more of right ventricular systolic pressure.

With myocardial restriction, diastolic pressures in the right ventricle and pulmonary artery are approximately equal to each other, as well as to mean pressures in the two atria and to pulmonary wedge pressure. The relationships are maintained during exercise, which raises the ventricular diastolic and the atrial pressures in the systemic and pulmonary circulations approximately equally. The majority of patients with the findings of cardiac restriction at catheterization prove to have pericardial disease. A small number

will be found to have myocardial disease often a primary myocardiopathy Harvey and associates studied the effects of digoxin and of exercise on the hemodynamic abnormalities of constrictive pericarditis They accepted the general postulate that in restrictive pericardial disease left and right ventricular diastolic pressures were equally elevated They pointed out that compression of the heart by a rigid pericardium was much more severe when hypervolemia and cardiac enlargement were present and that the hemodynamic abnormalities could in some instances be partially reversed by treatment for heart failure

Clinical diagnosis

General considerations

PERICARDIAL DISEASE Restriction of the heart by an abnormal pericardium should be considered as a possibility in patients with persistently elevated venous pressure with or without ascites and peripheral edema Frequently exertional dyspnea is an additional complaint Constrictive pericarditis or pericardial effusion should always be considered in the differential diagnosis of obscure heart failure especially of the right heart Constrictive pericarditis without calcification is more likely to be missed The examiner should be especially alert to this possibility when the venous pressure fails to fall satisfactorily with treatment for heart failure The more common causes of significant accumulation of liquid in the pericardium are tuberculosis and trauma but many cases are of unknown cause Collagen disease or metastatic neoplasm may be responsible Patients who have undergone attempted needle puncture of the interatrial septum and in whom the free wall of the right atrium has been perforated and those who have had diagnostic left ventricular puncture should be watched for increasing venous pressure and pulsus paradoxus They constitute a new and all too numerous group in which the possibility of cardiac tamponade must be anticipated [1] The same vigilance is called for and for the same reasons in patients with symptoms however mild attributable to thoracic aortic aneurysms and in patients who have been the victims of chest injuries Traumatic bleeding or effusion into the pericardium may be delayed [4] and a sense of security gained from the absence of signs when the patient is seen soon after the accident may be false Tuberculosis is the most common recognizable cause of constrictive pericarditis The diagnosis of tuberculosis calls for an evaluation of the pericardium and the presence of ascites whether or not tuberculous raises the possibility of pericardial thickening or effusion Nontuberculous infections of the pericardium may be accompanied by pericardial effusion and followed by constrictive pericarditis Constrictive pericarditis occasionally complicates adult rheumatoid disease [1] It may follow traumatic pericarditis [4] and irradiation of the chest and occasionally is a complication of idiopathic pericarditis[11,17] and rarely of histoplasmosis [18]

MYOCARDIAL DISEASE The compliance of the heart may be decreased in primary myocardiopathy or when the myocardium or endocardium is infiltrated by abnormal tissue The principal alteration in hemodynamics is decreased ability of the ventricles to expand during diastole so that filling is impaired and the clinical picture greatly resembles that of pericardial disease There are case reports describing the resemblance to constrictive pericarditis of subendocardial fibroelastosis [9,10] cardiac amyloidosis [11,1] cardiac hemochromatosis [12] fibrosis of the myocardium [11,11,14] and primarily myocardial disease [14]

THE VENOUS PULSE The venous pressure is elevated when the heart is compressed or stiffened by pericardial myocardial or endocardial disease The external jugular veins are distended and may pulsate but it is more important to inspect the neck the angles of the jaw and the ear lobes for pulsations of the deep jugular venous system [17] No single posture of the patient should be routinely adopted but the neck should be examined with the patient's thorax and neck elevated to that height which demonstrates the venous pulse most effectively Any posture may be the best from a few degrees above the horizontal to bolt upright and depends upon the height of the venous pressure The patient should be breathing as comfortably as possible with the head gently

turned until the venous pulse is most obvious and the neck muscles are relaxed. Elevation of venous pressure may be estimated by the height of the venous pulse above the sternal angle. Neither the *a* nor the *cv* waves are dominant in restrictive disease of the heart, but the positive waves in the neck are approximately equal in amplitude.[5,37] The *y* descent is rapid and its trough conspicuous,[5] and the *x* descent may also be rapid.[5] These findings are not diagnostic of pericardial disease but may equally well occur in restrictive cardiomyopathy.[38] The rapid *x* and *y* descents deny significant disease of the tricuspid valve or obstruction of the superior vena cava. The venous pressure may rise on inspiration[1] because the inspiratory increase in venous return cannot easily distend the right atrium. This phenomenon is called *Kussmaul's sign* and is of greater historical than diagnostic interest because it is frequently absent in pericardial compression and may be present in heart failure of many kinds.[5] When this sign is present, it often takes the form of absent inspiratory fall in venous pressure and not an actual increase during inspiration.

BLOOD PRESSURE AND PERIPHERAL PULSES. It is important to appreciate the fact that a patient with chronic constrictive pericarditis or chronic pericardial effusion may have a normal peripheral arterial pulse and blood pressure. Tachycardia, low arterial systolic pressure, small pulse pressure, and pulsus paradoxus are of great diagnostic importance when present, but their absence is not necessarily evidence against chronic restriction of the heart. These signs, although present in the majority of patients with acute cardiac tamponade, are absent in many patients with constrictive pericarditis or restrictive myocardiopathy. We have seen them develop minutes after inadvertent puncture of the free wall of the right atrium during attempted transeptal catheterization of the left atrium and spontaneously improve within an hour. Good bedside technique is essential for the proper demonstration of pulsus paradoxus. Labored breathing, especially with emphysema or bronchial asthma, is the most common cause of pulsus paradoxus. For this reason pulsus paradoxus should be measured with the patient breathing as quietly as possible. The difference between blood pressure readings when sounds are heard only in expiration and when they are heard throughout the respiratory cycle is the measure of pulsus paradoxus. Severe pulsus paradoxus is apparent to the finger examining a peripheral artery during normal respiration. Disappearance of the radial pulse during deep inspiration is probably significant of cardiac restriction, but lesser changes in pressure during exaggerated breathing are difficult to interpret.[37] Pulsus alternans[38] may complicate pericardial effusion in man, and we have seen it in dogs shortly after the induction of severe cardiac tamponade. It is readily reversible by the aspiration of fluid from the pericardium. Pulsus alternans may occur with or without electrical alternans[39] and with or without pulsus paradoxus.[5] Detection of it in the presence of pulsus paradoxus requires that blood pressure be examined during suspended respiration.

AUSCULTATION. With large pericardial effusions the heart sounds are sometimes distant, but this is by no means an invariable finding. In constrictive pericarditis and occasionally in tamponade, there may be an additional diastolic sound that frequently is called *the pericardial knock*.[31] It occurs earlier than a ventricular gallop, later than the pulmonary component of a split second sound, slightly later than most opening snaps, and coincides with the rise in ventricular pressure from its early diastolic dip.[31,39] It is frequently loud, sometimes louder than the heart sounds, and is snapping in quality. The sound is sometimes louder in inspiration and may be palpable. After pericardiectomy it disappears or becomes later and softer. Beck and associates[40] described an unusual form of splitting of the second heart sound in 4 cases of constrictive pericarditis. Splitting started at the very onset of inspiration and lasted for one or two beats only. Phonocardiograms showed that it was caused not by the normal inspiratory delay of the pulmonary closure sound but by early occurrence of the aortic closure sound at the onset of inspiration. Our own studies in dogs have demonstrated decreased left ventricular ejection during inspiration in pulsus paradoxus[34] and the observation of

Beck and associates suggests that this also occurs in man with constrictive pericarditis. Beck and associates found also that the pulmonary closure sound fell a fixed distance beyond the R wave of the electrocardiogram and concluded that normal inspiratory variation in right ventricular ejection is absent in constrictive pericarditis. This conclusion is not the only one that can be drawn from their data, since the volume of right ventricular ejection is not the sole determinant of the R-P interval. Right ventricular ejection volume that does not vary with respiration is not in accord with most experimental data on the mechanism of pulsus paradoxus.[?]

The heart sounds may become softer when the patient is examined prone and supported on his elbows instead of becoming louder as they normally do.[33]

OTHER MANIFESTATIONS. It was stressed earlier in this account that constrictive pericarditis impedes the filling of both ventricles. Consequently, there is pulmonary venous as well as systemic venous hypertension. Systemic venous congestion is more manifest than pulmonary venous congestion because the restricted right ventricle cannot so easily flood the lungs as it does when pulmonary venous congestion results from mitral stenosis or left ventricular failure. Fine basilar rales are usually inconspicuous and the lung fields are usually clear on roentgenograms. Cardiac contraction is limited by decreased diastolic filling and fiber length, but it is unwise to dismiss the possibility that cardiac contraction may be directly impeded by pericardial or myocardial restriction[14] or by attendant myocardial disease. Lindell and associates[?] found that intravenous histamine in 4 patients with constrictive pericarditis raised the stroke volume more than did exercise. They concluded that histamine directly increased the contractile power of the myocardium.

The concept that constrictive pericarditis exerts its effects on the circulation at the venoatrial junctions has been abandoned in face of many physiological and clinical studies, some of which have been reviewed here.[?] Of interest, however, are the isolated case reports of patients in whom localized bands of constriction about the valve rings caused clinical pictures simulating stenosis of the mitral and semilunar valves.[?]

In constrictive pericarditis and in pericardial effusion the apex beat is frequently impalpable or difficult to locate. The cardiac impulse may be diffuse or impalpable. Cardiac dullness may extend beyond the apex beat in those cases of pericardial effusion in which the apex beat can be felt.

Special studies

The electrocardiogram. The electrocardiogram in pericardial effusion may show low voltage because the electrical impulses from the heart are poorly conducted to the recording electrodes. The electrocardiogram may be normal, and the specific alteration of T waves ascribed to acute hemopericardium[?] are not very convincing. Electrical alternans with or without pulsus alternans may occur in pericardial effusion that is causing tamponade.[31] Complete electrical alternans involving the P, QRS, and T complexes is virtually diagnostic of pericardial effusion.[?] Incomplete alternans may be seen in either congestive failure or cardiac tamponade.[?] We have seen complete alternans in experimental acute tamponade in dogs and found it to be readily reversible by aspiration of some of the tamponading liquid. The electrocardiogram in chronic constrictive pericarditis is abnormal in the vast majority of cases.[?] There is widespread flattening or inversion of the T waves with isoelectric S-T segments and QRS complexes which are frequently of low voltage but which are otherwise normal. Atrial fibrillation is present in approximately one third of long-standing cases of chronic constrictive pericarditis[?] and is found in a similar proportion of the cases of myocardiopathy.[47] More complex arrhythmias, such as supraventricular tachycardia, ventricular tachycardia, and heart block, complicate a small proportion of the cases of myocardiopathy[?] and should warn against the diagnosis of constrictive pericarditis. Similarly, overt left ventricular hypertrophy, left or right bundle branch block, and abnormal Q waves very strongly suggest myocardial rather than pericardial disease.[?] Broad P waves are not uncommon in constrictive pericarditis and in

pericardial effusion.[illegible] It is fair to add that in many instances the electrocardiogram fails to distinguish between pericardial disease and myocardiopathy.

Radiologic findings

PERICARDIAL EFFUSION. Large pericardial effusion produces a very large cardiopericardial silhouette on the posteroanterior roentgenogram and usually the lung fields are clear. There is no characteristic shape of the heart whereby pericardial effusion may be distinguished from generalized cardiac enlargement, nor does a change in the shape of the heart shadow when the patient is tilted from the supine to the erect posture necessarily distinguish cardiac enlargement from pericardial effusion.[illegible] A large, poorly pulsating "water bottle" heart with obliteration of the normal contours which does not shrink during the Valsalva maneuver and whose base widens in the supine posture can at best only raise the possibility of pericardial effusion. On cinefluorography the epicardial fat may show as a thin radiolucency separating the myocardium from the pericardial fluid. When this sign is present it is very *helpful* in demonstrating pericardial effusion as distinct from generalized cardiac enlargement.[illegible] Special studies are usually necessary to distinguish pericardial effusion from cardiac enlargement. These include radioisotope scanning, angiocardiography, and the use of intravenous carbon dioxide. Radioactive albumin injected intravenously can be scanned over the chest.[illegible] The scan will be dense as far as the endocardial borders of the heart. Pericardial effusion will show as a radiodensity surrounding the heart with few or no scan dots. The patient is required to cooperate carefully for the meticulous positioning that is required. In other respects the procedure has the merit of simplicity but is somewhat insensitive. With the patient lying on his left side, 50 ml of carbon dioxide may be injected intravenously.[illegible] A film or preferably serial films taken in this posture a few seconds afterward will show radiolucency immediately beneath the right atrial wall. Pericardial effusion appears as a density between the lucencies of the carbon dioxide and the right lung. This procedure is simple and can be performed rapidly. It requires that the patient be able to lie on his left side and hold his breath. It can be recommended for patients who are acutely ill but who can cooperate to this extent. Another method employs radiopaque contrast material injected into the heart. Pericardial effusion appears as a hazy density surrounding the heavy density of the contrast material.[illegible] At fluoroscopy for this procedure it is helpful to direct the tip of the catheter laterally and run it up and down the lateral wall of the atrium. Normally the tip of the catheter appears to be at the very edge of the heart shadow. In pericardial effusion the tip cannot be brought to the outer border of the right atrium. Interpretation of these special studies is not always simple, especially when the pericardial effusion is not large. The carbon dioxide or iodinated contrast material in the heart is separated from the lung by endocardium, myocardium, pericardial effusion if any, and the pericardium, each or all of which may contribute to abnormally wide separation of the heart from the lung. In addition, right pleural effusion and disease of the lower or middle lobe of the right lung may obscure a pericardial effusion. As discussed earlier, acute pericardial effusions which produce cardiac tamponade, even when small, are usually recognized at the bedside. If circumstances permit cardiac fluoroscopy, the heart shadow may not be very large but cardiac pulsations are almost always diminished or absent.

CONSTRICTIVE PERICARDITIS. In chronic constrictive pericarditis diagnostic findings may be obtained from conventional radiologic studies. In some cases the heart is small or not greatly enlarged, pulsates poorly or not at all, and may be surrounded by a ring of calcium. The extent of calcification may be most evident in the oblique and lateral projections, particularly the left anterior oblique.[illegible] It should be recalled that calcification of the pericardium may occur without constrictive pericarditis.[illegible] In this circumstance it is less dense and more scattered, and the heart pulsates well at fluoroscopy. Care should be taken not to misinterpret calcification of the myocardium or of the coronary arteries as pericardial calcification.

The radiologic diagnosis of noncalcified constrictive pericarditis is more difficult

and is very important since calcification cannot be detected radiologically in 40 per cent of the instances of constrictive pericarditis. The heart is often normal in size or moderately enlarged and appears to pulsate little if at all, findings that are so nonspecific that they seldom give rise to the correct diagnosis if this has not been suspected before the radiologic examination. Considerable cardiac enlargement with tamponade implies that pericardial effusion is present and in constrictive pericarditis suggests that the disease is active.[5]

Angiocardiography may be helpful since the thickened pericardium can then be seen between the contrast-filled right atrium and the right lung. The normal pericardium as seen radiologically is 3 to 5 mm. thick. Abnormal thickness of the pericardium can also be recognized after the injection of carbon dioxide into the right atrium. Gross myocardial hypertrophy can also be detected by angiocardiography and may be confused with pericardial thickening. Myocardial hypertrophy appears as an abnormal density between the contrast material and the outer edges of the ventricles. The right atrium is unlikely to be sufficiently hypertrophied to appear unusually thick on angiocardiography or on a CO_2 contrast study, but a right atrium infiltrated by a disease process can attain the thickness of a diseased pericardium. In myocardiopathy, very gross hypertrophy of the papillary muscles may show on the angiocardiogram as irregular filling defects.[17]

Paracentesis of the pericardium. Pericardial tapping is frequently needed for general diagnosis, etiological diagnosis, or for therapy of pericardial effusion. This procedure is attended by the hazards of myocardial laceration, puncture of a coronary vessel, and arrhythmia. Except in life-threatening emergencies it can no longer be reasonably regarded as a safe bedside procedure because modern monitoring and resuscitation equipment, the availability of an anesthetist and of personnel skilled in transcardiac catheterization techniques prevent most of these complications or render them readily reversible when they do occur. Pericardiocentesis is best carried out in the cardiac catheterization laboratory, or in the special procedure room of a department of radiology, or in the operating suite, depending upon local circumstances. The xiphisternal or anterior approach may be employed according to the preference of the operator. Facilities for endotracheal anesthesia, electrocardiographic monitoring of the patient and of the position of the aspirating needle,[44] electrical control of the heartbeat, pressure monitoring, and thoracotomy should be immediately available. When grossly bloody fluid is aspirated, the needle should be attached to a pressure transducer in order to verify that the tip of the needle lies in the pericardial space and not in one of the ventricles or in an artery. At the time of aspiration, sufficient material should be obtained and placed in suitable containers for cytological, histological, bacteriological, hematological, and clinical studies so that an unnecessary repetition of the puncture may be avoided. When the fluid is grossly bloody, its hematocrit should be compared with that of the patient's venous blood. Prompt clotting implies that the blood was drawn from a cardiac chamber and not from the pericardial space. After pericardial fluid has been aspirated, carbon dioxide may be injected into the pericardial space and films may be promptly made to delineate the thickness of the pericardium.

Summary

Restriction of the normal range of motion of the myocardium produces a consistent pattern of hemodynamic and clinical events. The features are similar whether the limited cardiac action results from cardiac tamponade, constrictive pericarditis, or restrictive myocardiopathy. Persistent elevation of systemic venous pressure, prominent jugular *x* and *y* waves, and paradoxical arterial pulse may be present with any one of these disorders. Intracardiac pressures may be similar, with narrow pulse pressure in the right ventricle, an early diastolic dip in both ventricles, and approximately equal right atrial and pulmonary wedge pressures. On physical examination, evidence of right or left ventricular hypertrophy, atrial and/or ventricular gallop rhythm, or murmurs of relative mitral or tricuspid insuf

ficiency support a diagnosis of myocardial disease rather than pericardial disease. A diagnosis of myocardiopathy is favored by an electrocardiographic pattern of bundle branch block, Wolff Parkinson White syndrome or left ventricular hypertrophy. Although routine roentgen studies are often of no diagnostic value, contrast studies with cardiac radioisotope scanning, intravenous CO_2 or angiocardiography will usually permit distinction between pericardial and myocardial disease. In rare instances the diagnostic problem cannot be resolved without resort to exploratory thoracotomy.

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Alan F Lyon

Diuretic therapy Part IX Ethacrynic acid

*Robert J Sperber M D**
*Arthur C DeGraff M D***
*Alan F Lyon M D**
New York N Y

Ethacrynic acid an aryloxyacetic acid is a new and very potent diuretic structurally unrelated to other diuretics It is still under investigation and not yet marketed but may be the most important therapeutic chemical agent developed for use in the management of pathologic retention of fluid since the introduction of chlorothiazide

Mode of action Ethacrynic acid is effective parenterally in dogs and man but is ineffective in rats It has been shown that ethacrynic acid reacts with and binds sulfhydryl groups in the distal renal tubular cells This occurs in vitro and has been demonstrated by histochemical techniques in catheterized dogs It has been further shown in catheterization studies that the kidney infused with ethacrynic acid is the one that diureses and that such a diuresis is associated with a decrease in protein bound sulfhydryl groups in that kidney This action appears to be similar to that of mercurial diuretics mercurials however do not cause a measurable diminution in the sulfhydryl groups In both instances the reaction is thought to interfere with enzyme activity

Although the histochemical technique demonstrating depletion of the sulfhydryl groups suggests that the distal tubules are the site of action of ethacrynic acid functional studies under conditions of water diuresis and hydropenia indicate that the action may be either on the distal tubules or the ascending limb of Henle s loop Either could account for both the decrease in the clearance of free water and the rise in the volume of solutes and urine that occur Under still other conditions of study reports have favored both the proximal and the distal nephrons as the site of action More studies will be required before the mechanism of action is fully understood

As with mercurials sodium and chloride are the urinary electrolytes principally excreted The loss of potassium is generally proportional to the increased volume of urine As with mercurials and thiazides patients who are avid retainers of sodium will excrete relatively more potassium There is no increase in the excretion of bicarbonate

Clinical experience All investigators have recognized ethacrynic acid as a powerful oral diuretic It is relatively well tolerated by mouth and rarely causes gastric distress and diarrhea There is no evidence that these side effects can be circumvented by parenteral administration

Unlike the thiazides many of which have an effect over a 24 hour period ethacrynic acid even when given orally

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*[illegible] Therapy Research [illegible] Bronx N Y [illegible] Hospital [illegible] West Kingsbridge Road Bronx N Y 10468
**Department of Therapeutics New York University School of Medicine [illegible] Avenue New York N Y 10016

induces a diuresis which begins within a half hour and is complete within 6 hours. Thus, the response to ethacrynic acid is more like the response to a parenteral mercurial, that is, intense and relatively brief.

Diuresis can be gradual or overwhelming in intensity, depending on the circumstances. Generally, the diuresis is related to the dose, and adequate clinical results have been produced with doses as small as 25 mg. daily or three times a week. On the other hand, in some cases doses of 100 to 150 mg. twice a day may be required to produce an effective diuresis. Since the response to oral administration is complete within 6 hours, the effectiveness of the selected dose can be ascertained in that period of time and an adjustment made. In a single maximal dose, ethacrynic acid is as potent as a mercurial, and since it can be given repeatedly, it must be considered to be the most potent oral diuretic available.

In patients refractory to all other diuretics, either alone or in combination, ethacrynic acid has often been effective even in small doses. It is in just such patients, however, that the dangerous problems of excessive loss of fluid have occurred. A loss of 12 to 15 pounds overnight after administration of ethacrynic acid has been reported in patients refractory and unresponsive to other diuretics, and instances of sudden death have occurred after such effective diuresis. It is paradoxical that these patients who have the most fluid to lose can, when finally given an effective diuretic, diurese so vigorously that the results are disastrous.

Side effects. The continued daily use of ethacrynic acid in ambulatory patients has infrequently produced fluid and electrolyte disturbances. Compared to the frequent hypokalemia in patients on thiazides who avidly retain salt, this complication with ethacrynic acid is quite infrequent. In fact, the instances of transient hyponatremia and hypochloremia, usually self-correcting, have been more notable than hypokalemia. The ambulatory patient in most cases is not so edematous as the hospitalized patient, and therefore is less likely than the latter to have a massive diuresis. In the hospitalized patient, hypokalemia has definitely occurred. As with the use of other oral diuretics, hyperuricemia has been frequent, and clinical gout has occurred occasionally. The effect of ethacrynic acid on blood sugar has not been adequately studied. Slight elevation of the blood urea nitrogen has occurred in a few patients, and the serum bicarbonate has become elevated in others. Liver function tests have not been altered as a result of treatment with ethacrynic acid. In our experience, abnormalities in the cellular constituents of the blood have not occurred in patients treated for a number of months with ethacrynic acid. There are unpublished reports of 3 cases of neutropenia or agranulocytosis in critically ill patients on a variety of drugs including ethacrynic acid. Although ethacrynic acid was not clearly implicated, frequent blood counts are presently advised. Frequent urinalyses have demonstrated no gross changes.

When ethacrynic acid becomes generally available, the physician will have still another effective oral and parenteral diuretic. To the patient who becomes refractory to all other diuretics, it extends the possibility of successful treatment. However, there are patients who are refractory to this agent also, and it must be remembered that the extreme potency of this new diuretic in itself may contribute to the patient's death, so that great care must be exercised in its use.

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Cineangiocardiography in hemorrhagic shock*

There has been recent interest in the condition of idiopathic hypertrophic subaortic stenosis as defined by the presence of a systolic ventricular pressure gradient in the absence of persistent anatomic obstruction.[1,2] A somewhat analogous situation was demonstrated by Gauer[4] in experimental hemorrhagic shock in dogs. This work was confirmed in our laboratory, although we emphasized that the gradient was between the apex and body of the left ventricular cavity rather than in the subaortic area. More recently we have extended these studies by biplane cineangiocardiographic observations in intact anesthetized dogs. These have shown a characteristic alteration in the configuration of the left ventricular cavity during hemorrhagic shock which affords an explanation for the recording of unusual ventricular pressure in these dogs.

A pressure gradient ranging from 150 to 300 mm. Hg developed in the apical region of the left ventricle 30 to 45 minutes after the establishment of hemorrhagic shock in a series of intact anesthetized dogs. The recordings of pressure were made with a Gauer manometer and the level of shock was maintained at 35 mm. Hg. Cineangiocardiograms taken at this time revealed the striking changes in the size and shape of the left ventricular cavity illustrated in Fig. 1. There is marked decrease in the end-diastolic (*D*) and end-systolic (*S*) volumes after 1 hour of shock (right half of illustration) as compared with the volumes during the initial control period (left half). The relative prominence of the coronary arteries during shock may also be noted as an incidental finding. In addition it can be seen that systolic contraction obliterates the apical portion of the cavity. A residual spot of dye marks the apex (arrow) and shows that the apical basal dimension has not changed significantly. This obliteration of the apical region occurs rapidly during early systole and remains so until subsequent diastolic filling. The result is prolonged isometric contraction of this region of the ventricle. This could explain the high pressures recorded from this site since the recording catheter is caught between the approximated muscular wall and its distal tip, for all practical purposes, within a closed chamber. In fact, in one cineangiocardiographic recording a prominent distal chamber of this sort was demonstrable.

In previous studies of shock we have observed that the onset of the systolic pressure gradient occurs as a terminal systolic spike in the ventricular pressure curve. As the state of shock continues this terminal systolic pressure gradient begins to occupy a longer period of systole until it finally is present throughout systole. Although our cineangiographic data are not yet complete on this point, the progression of the changes in the apical systolic pressure tracings probably reflects the parallel progressive systolic obliteration of the apex as the period of shock is prolonged.

These hemodynamic features of shock may also help to explain the prominent subendocardial lesions that have been described in the hearts of dogs in shock. The actual mechanical trauma to these regions produced by the prolonged period of contact of the contracting myocardial surfaces could play an important role. In this situation one would not expect a beneficial effect from a drug such as noradrenalin which increases the contractile force of the heart and thus augments the insult. Previous studies have, in fact, demonstrated a deleterious effect of noradrenalin when used to treat dogs in hemorrhagic shock.

A. M. Martin, Jr., M.D.
D. B. Hackel, M.D.
Madison S. Spach, M.D.
M. P. Capp, M.D.
E. Mikat, A.B.
Duke University Medical Center
Durham, N. C. 27706

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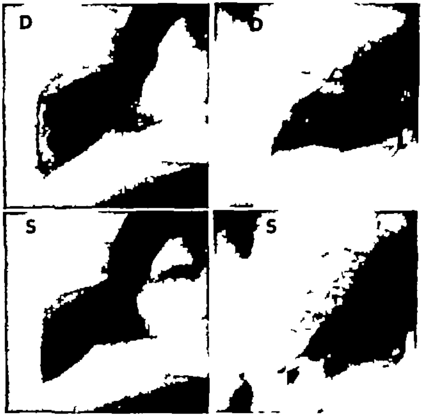


Fig. 1. Cine n or d ram at end-dia tole (D) and end systole (S). Left k d ol mn Contr l period. Right hand col mn After one hour of shock.

H O I tr tr lar pres ure h me in k d tr hem rrh g h k Fed I c 22 5 1X3

6 H k l D B an I C d I W I Iffect f hem rrha h k n the he rt n l rculati f t t d C lat 11 8 1955

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Victims of the vector

Vectorcardiography h ll d ignificant inform t n to our un ler tan ing f the lectrical fiel f the heart actic curre t l t electrocardi raphy in general One f the t ta l ng contrib t ns t vectorcard r ph w the f ln of Iurch and h lleagu s that l tes in the vector loop in l ate areas f l e lized myocard al fibros les and th m tial infarct ectors However a we will l ustrat the ind scrim nat use of ector cardiography l those wh ha n imperfect understa l g of the l ject even th u h they be competent l nical ardio t a fra ht w th dan er

Recently two pparently healthy male sul jects in their forties applied for life insurance. In both cases a diagnosis of myocardial infarcti n had been made 2 years previou ly based solely on their vectorcardiogram. The twel lead conventional electrocardiograms were and are quit normal. The symptoms in each case had been very va ue atypical chest pain without any clinical substanti ation of a myocardial infarct. In both cases the individual w con idered by his atten ing phy sician to be the victim f a infarct on the ba is of the vectorcardiographic diagnosis.

Exam nation of the vectorcardiograms which

had been obtained by these physicians whose name were unfamiliar to me failed to substantiate the diagno of infarction In one case it was presumed by the attending physician that the horizontal plane loop showed an inadequacy of leftward di rected forces which supposedly indicated a lateral wall infarct whereas in my opinion the horizontal plane loop was within the range of normal varia tions and Leads V V and V had no Q waves and had good healthy R waves There were no S T or T abnormalities

In the other case of incorrect diagnosis the sub ject was supposed to have an antero eptal infarct because of the lack of rightward and forward d rected initial forces Examination of the vector card ogram di closed an unusually large blob of light at the origin which could easily have hidden normal small rightward and anteriorly directed initial portions of the loop The attending physician overruled the fact that there were normal R waves in Lead V V and V and relied instead on his impression of the ectorcardiographic find ngs

Because of our experience with these two cases we as ume that there must be others in which equivocal vectorcardiogram have taken an un warranted precedence over the normal well es tablished twel lead electrocardiogram We believe that the u e of the vectorcardiogram to e tablish a final diagnosis by a physician who is not thoroughly knowledgeable and highly experienced in he field of vectorcardiography is not only a waste of time but can do gra e inju tice to the patient

Paul H Lan ner Jr M D F A C P
4601 Market Street
Philadelphia Pa

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Continuous electrocardiographic monitoring in acute myocardial infarction

In the first few days after cute myocardial infarc tion sudden unexpected death is common External cardiac massage and external electrical defibrillation have been shown to be effective in the resuscitation of some patients with circulatory arrest after myo cardial infarction However for success these measures must be instituted promptly There are now several reports of ontinuous electrocardio graphic monitoring in an intensiv care area a routine management for patients w th acute myo cardial infarction I the routine use of continuous electrocardiographic monitoring after acute myo cardial infarction of value I it of direct benefit to the patient and does t lead to a reduction in mortality

W have studied 87 unselected male patients with acute myocardial infarction Electrocardio graphic monitoring and special nursing were con tinued until 72 hours after the last epi ode of chest pain or until any gnifica t arrhythmia was con trolled or terminated[1] At the time of adm ssion the clinical state of the patient was classified into one of three groups according to a modification of the criteria of Fries and associates e (1) mild (2) sev re and (3) card ogenic hock The diagno f cardiogenic hock required fulfillment of the criteria of Binder and associates

The group w th mild infarction consisted of 37 patients I this group there w 1 death it oc curred fter the period of mon toring 15 days after farction and was sudden and unexpected During the period of monitoring 3 patients with clin cally mild myocardial infarction developed ventricular fibrillation and died All were succes fully de fibrillated and have returned to their usual occupa tion This succes ful re uscitation of the e patients reduced the mortality in this group from 11 to 3 per ce t

The group w th severe infarction consisted of 42 patients in thi group there were 22 deaths (52 per cent) There were no long term surv ors following re uscitat on after cardiac arrest During the period of monitoring sudden circulatory arrest occurred in 12 patient (28 per cent) it was due to entricular fibrillation in 7 and to asystole in 5 Resu citation was commenced immediately in all cases but succe was limited Of those with asystole cardiac action was restored in 2 However one died n renal failure 11 day after infarction the other made excellent progress but died uddenly 17 days later I 2 of the 7 patients w th entricular fibril lation external electrical defibrillation resulted l m ted survival In one 1 was prolonged 5 days during wh ch t me there were three add tional iso lated epi odes of entricular fibrillation from which he was resu citated the other li ed onl 2 hours afte the in tial defibrillation I the other 5 patients th entr lar fibrillation el ctr cal def brill tion w s followed by usta ned y tole or by lo ve t tricular rh thm ith g ly widened b zarre QRS omplexe and ardiac actic co ld not b restored

After the period of monito ng dd ti nal 7 patient the group with severe infar tion su

tained sudden unexpected circulatory arrest. This occurred at times ranging from 8 to 21 days after infarction. After some initial delay, electrocardiograms were obtained in 5 and all showed ventricular fibrillation. Only 1 of these patients was successfully resuscitated but he died 5 days later.

In 3 other patients from the group with severe infarction death was not unexpected, occurring after the period of monitoring and due to renal failure.

There were 8 patients with cardiogenic shock and all died. Seven of these died during the period of monitoring. Circulatory arrest in each was due to asystole; immediate resuscitation was attempted in all, but with no significant success. The eighth patient recovered from the shock state but died 9 days after infarction; there were no data on the mode of collapse and resuscitation was not attempted.

There was a total of 31 deaths, a mortality of 35 per cent. Of the 56 who survived the acute attack, 36 had mild and 20 had severe infarction. These survivors have been followed for periods of to 16 months. All have returned to their normal pattern of life except for 3 patients with severe infarction who have required a further period of general inpatient care because of cardiac decompensation. There have been no ill effects from continuous electrocardiographic monitoring and intensive care; in particular, anxiety states have not resulted.

Continuous electrocardiographic monitoring has given a clear picture of the high frequency of cardiac arrhythmias during the early days after acute myocardial infarction. Analysis of the recordings in our 8 patients showed that 66 developed significant change in cardiac rate, rhythm, or conduction, an incidence of 6 per cent. Many of these disturbances were transitory and did not require treatment. However, in some patients the severe arrhythmias which developed during the period of monitoring were detected and treated promptly. We believe that some of these patients may have died if monitoring had not been in progress at the time of onset of the arrhythmia. The most notable example was a patient (Case 29) in the group with severe infarction who had seven episodes of supraventricular tachycardia, five of ventricular tachycardia, and one of ventricular flutter.

Minogue and associates reporting on 9 long-term survivors among 60 patients who had cardiac arrest after acute myocardial infarction stress the necessity of early detection of circulatory arrest if a successful outcome is to be achieved. Our experience suggests that when extensive myocardial damage has occurred, resuscitation from cardiac arrest, even when commenced immediately, is unlikely to be successful. In patients with cardiogenic shock myocardial damage is often gross. Although continuous electrocardiographic monitoring displays the arrhythmias that such patients frequently develop, it does not improve the prognosis. Asystole appears to be a terminal event in a myocardium which can no longer contract effectively.

Sudden circulatory arrest occurred in 45 per cent of our patients in the group with severe infarction. This was most common in the first 3 days after infarction, but occurred up to 3 weeks after infarction. Continuous electrocardiographic monitoring will allow prompt detection of cardiac arrest; however, it is impractical to continue monitoring for prolonged periods in order to detect the onset of late cardiac arrest. Cardiac resuscitative measures have yielded no long-term survivors from our group with severe infarction. Autopsy has confirmed the presence of extensive myocardial infarction in these patients. However, Minogue and associates have reported long-term survival after asystole in a woman with acute myocardial infarction and pulmonary edema. Patients with clinically severe myocardial infarction are critically ill; they frequently develop serious arrhythmias and they may benefit from intensive care and continuous electrocardiographic monitoring. A clear answer on the value of continuous monitoring in these patients will be available when a larger number has been studied.

Continuous electrocardiographic monitoring has the most to offer in cases of clinically mild acute myocardial infarction. Cardiac arrest in these cases was most common early after infarction. With less myocardial damage, if cardiac arrest is detected and treated early, a successful long-term outcome can be anticipated.

Thus, in the early stages after acute myocardial infarction, continuous electrocardiographic monitoring with efficient resuscitative service is of value as a routine method of management in mild cases and possibly in severe cases. For best results, monitoring must be performed in an intensive care area where all drugs and equipment required in cardiac resuscitation are immediately available. A specially trained staff must be in attendance to evaluate changes in the cardiac rhythm and commence external cardiac massage as soon as cardiac arrest occurs.

James S. Robinson, M.B.B.S., M.R.A.C.P.
Research Assistant, Cardiac Department
Royal Melbourne Hospital
Victoria, Australia

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La mort d'amour

Although widely recognized in song and story, *la mort d'amour* has received relatively little attention in the medical literature. Dr. George X. Trimble has recently pointed out the singular lack of reported cases, fatal or otherwise, of acute coronary insufficiency following or during sexual intercourse. The reluctance of persons involved and their physicians to provide accurate documentation of this phenomenon is understandable.

In 1957 an autopsy was performed in this department on a 23-year-old soldier, a veteran of Korea, who died while in bed with a woman of questionable character. He was a muscular 200-pounder with a 470-gram heart. The coronary arteries displayed severe atherosclerosis and luminal stenosis but no total occlusion was discovered. Fresh and old infarctions were present in the myocardium.

That the stress of coitus imposes an increased work load on the heart has been readily demonstrated. The epidemiology and prophylaxis of coronary attacks precipitated by sexual activity pose real problems in a population with an increasing incidence of atherosclerosis and leisure time.

B. Alexander [illegible], M.D.
Departments of Pathology
Ottawa General Hospital and
University of Ottawa Faculty of Medicine
Ottawa, Ontario, Canada

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Letters to the Editor

Cardiac Unit and
Department of Medicine
Negev Central Hospital
Beersheba, Israel
June 24, 1964

To the Editor:

Dr. Dimosi, in his recent publication on unusual forms of second-degree A-V block (AMERICAN HEART JOURNAL 67:150, 1964), has expressed interest in the possibility of Mobitz Type II block occurring independently in patients who never experienced the M-A-S (Morgagni-Adams-Stokes) syndrome. We had the opportunity to observe this in two such patients in the past 4 months.

The first patient was a 70-year-old woman who had been hospitalized for dizziness and low pulse rate of 4 days' duration, accompanied by frequent vomiting and uremia. The admission ECG showed complete A-V block with an atrial rate of 95 per minute and ventricular rate of 37 per minute. This was later replaced for a short bout of supraventricular tachycardia of 140 per minute with a 2:1 block, P-R of 0.13 second, and a ventricular rate of 70 per minute. Later on this turned to a sinus rhythm of 130 per minute with second-degree block and a fixed P-R of 0.13 second and returned shortly before discharge to normal sinus rhythm with a rate of 100 per minute. The patient's consciousness was blunted at the time of admission, probably in relation to the high blood urea nitrogen, which returned to normal during the hospital course. She never experienced the M-A-S syndrome.

The second patient was an 18-month-old child who was hospitalized because of severe congestive failure due to endocardial fibroelastosis. Her ECG on admission showed nodal tachycardia of 260 per minute with reversed Wenckebach phenomenon intermittently, with retrograde conduction. The child was fully digitalized with digoxin during the next 6 hours. Twelve hours later the ECG showed sinus tachycardia with a rate of 150 per minute with a P-R of 0.11 second and changing Mobitz Type II second-degree A-V block—5:6 to 6:9:8. The patient died 4 hours after admission.

It has been stated that the Mobitz Type II block has not been recorded as a sign of digitalis overdosage. Since our small patient was fully digitalized in a short period of time and since the myocardial damage revealed by necropsy was so severe we were inclined to believe that the A-V conduction abnormality was possibly related to digitalis.

The frequency of the Mobitz Type II block is difficult to establish; moreover, apparently this abnormality does not always carry a serious prognosis. It is possibly justified to admit that the underlying heart disease and the presence of the M-A-S syndrome determine the future of the patient with Mobitz Type II second-degree A-V block.

Uriche Gueron, M.D.
Jacob Ben . . ., M.D.

Department of Medicine
The Mount Sinai Hospital
Fifth Ave. and 100th Street
New York, N. Y. 10029
November 16, 1964

To the Editor:

We appreciate learning of the two cases of Mobitz Type II block. Since there are so few reported in the literature, each case is worthy of study.

The first patient had an electrocardiogram indicating complete heart block with a complaint of dizziness on admission, and this may well represent an equivalent of the Adams-Stokes syndrome. The period of observation in this patient was too short to draw final conclusions. The second patient had fibroelastosis, which has been found occasionally to produce heart block. Therefore, it is difficult to know whether the digitalis was the cause of the heart block. We agree that the prognosis of patients with Mobitz Type II block is dependent on the underlying heart disease.

Ephraim Donoso, M.D.

Announcement

The American Ballistocardiography Research Society and European Ballistocardiographic Research Society are jointly sponsoring the FIRST WORLD CONGRESS ON BALLISTOCARDIOGRAPHY AND CARDIOVASCULAR DYNAMICS on April 1, 13, and 14, 1965, in Amsterdam, Netherlands.

The congress represents a fusion of the 5th Congress of the European Society for Ballistocardiographic Research and the 10th Annual Meeting of the American Ballistocardiography Research Society.

The central theme deals with the significance of ballistocardiographic examination, especially in comparison with other cardiovascular methods of examination. Physiological, clinical, and physical aspects will be considered.

The European secretary is Dr. A. A. Knoop, Physiological Laboratory of the Free University, Vlampl. 11, Amsterdam, Netherlands.

American Heart Journal

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Editorial

The use of hyperbaric oxygen

*I. Boerema, M.D.**
Amsterdam, Netherlands

Our first communications concerning the introduction of hyperbaric oxygen as an aid in surgery at the European congresses on cardiovascular surgery and cardiology in 1956 in Zurich and Stockholm were received with great interest. However, apart from the Glasgow group who presented their first paper in 1958, we had no followers. Only quite suddenly since 1961 has interest in the new idea risen to such great heights that in several centers throughout the world, first of all in the United States, people have started to build high pressure chambers.

The enthusiastic reception of the idea but slow acceptance of the practical applications needs to be explained. First of all, some resistance to leaving a normal operating room to work inside a closed steel tank had to be overcome. Indeed, when we started our work in a small tank of the Royal Dutch Navy School, we were rather nervous when working inside, and some of us suffered from claustrophobia. However, this nervousness abated after a few sessions in the tank, and our concentration at work was quite normal.

Secondly, it was the belief that working in high atmospheric pressure would mean danger. Indeed it does, since there is the danger of rupture of the eardrums; there is at times terrible pain in the nasal sinuses and the danger of oxygen intoxication and of decompression illness exists. All these dangers, however, can be overcome safely when adequate preventive measures are taken.

During the increase in the pressure, pain in the ear is normal and can be easily overcome by swallowing or by the Valsalva maneuver. However, in some people the pain remains, mostly when the pressure has reached a level of 5 meters of water; then a man has to leave the tank and return quickly to normal pressure. It may happen that the same person has no trouble the next time, but if this occurs several times, such a man is unfit for working in the tank. Spraying of the nasal and pharyngeal mucous membrane with adrenalin may help, but as a rule it seems safer that this man abandon his work in the tank.

In the case of children, or of patients in narcosis, or of patients who needed urgent treatment in the tank, a simple perforation of the eardrum was made by the E.N.T. specialist. We saw no harm in this simple procedure.

We worked hundreds of times inside the tank at a pressure of 20 meters of water, that is, 3 atmospheres absolute, and felt quite normal and did our work well. We were not aware of being in any danger

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*University of Amsterdam, Amsterdam, Netherlands.

toms of decompression illness one of these had some pain in a shoulder and the other one had blurring of vision for some minutes Both were recompressed and apparently no harm was done However both these people were doctors anesthetists both had a rather thick layer of fat and both were seated on a stool beside the patient's head during the decompression Probably the circulation in the layers of fat of the compressed buttocks was so limited that the stored N_2 gas was not transported away so that bubbles were formed when the doctors got up after the decompression was completed Since then everybody in the tank has to be on his feet and make several movements during the decompression We have seen no cases since then

Thus prevention of decompression illness is very important and must be taken into account in the construction of the chamber The workers inside the tank feel quite normal and are not aware of any danger at all so that they are inclined to underestimate the danger of decompression and to shorten the length of time necessary for decompression Indeed the decompression time is rather annoying When the workers were allowed to decompress themselves several cases of decompression illness occurred For that reason we decided to build our new large chamber in such a way that the workers would be absolutely unable to decompress themselves They have to phone to the technician outside and to ask for decompression This technician is not allowed to shorten the decompression time for any reason The steplike decompression scheme of Haldane is followed strictly Since the workers inside are completely dependent on the technician outside and since something might happen to this man there are always two well trained technicians at the switchboard These two men are on duty 8 hours a day and since very often the chamber is used at night for emergency cases we needed a personnel of 6 men all well trained in working with hyperbaric conditions This is the heaviest part of the financial burden of operating a hyperbaric unit The cost of our unit consisting of a large operating room (floor surface 4 by 6 meters) and a large lock heavy foundations the machinery the heating the rooms for pretreatment and for scrubbing and the wooden house around it was nearly one hundred thousand dollars

Even when a university hospital like ours does not intend to operate on a profit basis we are glad to be able to say that we have well regained our cost for instance we saved the life and the limbs of a 28 year-old man who was sent to us as a completely hopeless case of gas gangrene after an accident to both of his legs This man was insured by the government if he had died as surely he would have had he not been treated with hyperbaric oxygen his young wife and four little children would have claimed a payment of twenty thousand dollars in insurance money This is only one of more than 40 cases of anaerobic infections most of them apparently hopeless cases which were sent to us and treated successfully

Originally we built our large chamber as a real operating room for we thought that hyperbaric oxygen drenching would be an aid in cardiac surgery But then we found that this principle was an excellent aid in several diseases These other uses soon proved to be of even more value than the gain in cardiac surgery and we think therefore that after our first publication especially on the remarkable success in the treatment of patients with infections of *Clostridium welchii* in 1960 the great interest in our work from all over the world really started However for treatment alone a much smaller room would be sufficient but it should be large enough to admit a patient accompanied by one or two doctors Since many of the patients who are brought into the tank for the first time need instruction and control and since some patients are comatose and may start vomiting we think that leaving the patient alone in the chamber is not advisable

Thus it seems to us that a large chamber ready for operative surgery on patients or on experimental animals is necessary in large or special medical centers smaller chambers ready for emergency cases such as acute vascular occlusion circulatory disturbances in the foot in open fractures or in cyanotic flaps of the skin after trauma or plastic surgery acute pulmonary

embolisms, acute coronary occlusion, carbon-dioxide intoxication, and clostridial infections should be available in geographical districts with a radius not over 100 miles. Patients have been sent to us often in a most serious condition by ambulance from various places in Holland, some located as much as 150 miles from Amsterdam. In no case did we have the impression that such transporting had done any harm to the patient. Although the chamber often is in use 24 hours a day, 7 days a week, it has until now fulfilled adequately the needs of a dense population of 12 000 000. We should prefer to have a second chamber for our septic cases, although many samples taken from different points in the chamber did not show more organisms in this room than in our normal operating room, and so far there have been no cases of infection after sterile operations performed in the chamber. Thus from a practical standpoint it seems to us that in the near future two chambers per 10 million dense population will be sufficient. However, we know that the fields of theoretical research and practical application are broadening rapidly, so that the demand for high-pressure chambers may surpass the figures mentioned above.

We never apply hyperbaric oxygen drenching to a patient for longer than 2 hours and never use pressures over 20 meters of water (i.e., 3 atmospheres absolute). However, investigations should be made to determine what effects higher pressures will have on the patient and on his disease; nothing is known about the limits of the exposure times for sick people. We know that the danger of oxygen intoxication quickly increases with the increase in the pressure of the oxygen. Whether this also means that the therapeutic value for some diseases will increase with still higher pressures is at present completely unknown, and has to be investigated.

So it might be wise to build the new tanks in such a way that they are safe for a still higher atmospheric pressure. Although our chamber was never used for pressures higher than 3 atmospheres absolute, it is still safe for pressures of 4 atmospheres. However, research seems to be needed in oxygen pressures of 5, 6, or even 7 atmospheres. And the safety limit of the tank cannot be changed once the apparatus is built. In an operating room this very high pressure will hardly be necessary, because the length of time available for the operation during hyperbaric oxygen drenching decreases very rapidly at pressures higher than 3 atmospheres; no operation can be performed within such short time limits. However, for the treatment of different diseases, tanks which can stand higher pressures might prove to be of great value.

Clinical communications

The role of bradycardia in the retention of sodium and water in complete heart block with and without heart failure in human beings

Charles K. Friedberg, M.D.
Ephraim Donoso, M.D.
William G. Stein, M.D.
Melvin Kahn, M.D.
Robert Litwak, M.D.
New York, N. Y.

Complete heart block may be accompanied by congestive heart failure which is often severe and refractory to diuretic therapy. The importance of the slow ventricular rate is indicated by observations that spontaneous reversion to normal sinus rhythm[1] or artificial induction of a more rapid ventricular rate[2,3] may be followed by significant diuresis and the disappearance of the clinical manifestations of congestive heart failure. Although bradycardia may be presumed to be a factor in the pathogenesis of this form of heart failure, it is not the sole factor, since heart failure does not invariably occur in patients with complete heart block despite similar slow idioventricular rates. The purpose of this study is to investigate the role of bradycardia, as well as other possible factors, in the pathogenesis of heart failure in patients with complete heart block by determining the maximum daily sodium excretory capacity during idioventricular rhythm and after an increase in the ventricular rate by implantation of a cardiac pacemaker.

In an acute study of 2 patients with complete heart block, one of them with congestive heart failure, Humphries and associates[4] found that the cardiac index, glomerular filtration rate (GFR), and effective renal plasma flow (RPF) were unchanged when the heart was paced at faster rates. However, no report was made on the excretion of salt and water or the induction of a diuresis with the faster paced rates. Stack and associates[5] found the GFR and RPF to be diminished in 3 patients with complete heart block but without clinical heart failure or evidence of intrinsic renal disease. Faster heart rates were not induced in these patients, and thus the contribution of the bradycardia to the altered renal hemodynamics cannot be evaluated. Other investigators[6,7] have been concerned with the relation of the cardiac output to various controlled ventricular rates in patients with complete heart block, but without relation to renal function or excretion of salt.

Material and methods

Four patients between the ages of 62 and 68 years, 3 of them with complete

From the Division of Cardiology, Departments of Medicine and Surgery, The Mount Sinai Hospital, New York, N. Y.
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Address: The Mount Sinai Hospital, 100th St. and Fifth Ave., New York 29, N. Y.

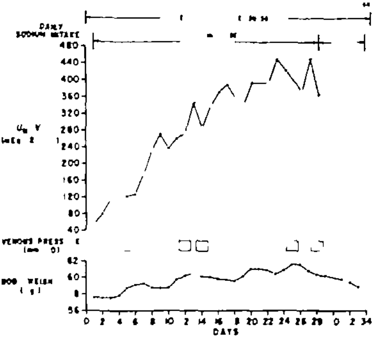


Fig 1 Case 1 64 year-old man Complete heart block No heart failure Normal maximal daily excretion of sodium (440 mEq) with progressive increments in intake of sodium to 453 mEq daily

heart block and 1 with advanced or complete heart block of 2 to 8 years duration were studied Two of the 4 had overt heart failure at the time of the study and the other 2 had no clinical evidence of cardiac decompensation Three of the 4 had suffered recurrent attacks of Adams Stokes syndrome

During the period of bradycardia each patient received a measured daily intake of sodium in the amounts indicated in the individual case reports and adjusted according to the presence or absence of congestive heart failure Water was permitted ad libitum The 24 hour urinary excretion of sodium chloride and potassium and the 24 hour endogenous creatinine clearances were determined each day The GFR referred to in the text was the average of 14 to 34 determinations The patients were weighed daily Venous pressures were measured when indicated At intervals of 3 to 5 days if the body weight had remained stationary the intake of sodium was increased progressively until either heart failure or gastric intolerance developed After a cardiac pacemaker had been implanted the above mentioned procedure was repeated following an adequate postoperative recovery period In one of the patients comparative studies were made before and after insertion of a cardiac catheter pacemaker instead of an internal cardiac pacemaker

Results

Case 1 (Fig 1) A 64 year old man with angina pectoris and complete heart block had been subject to Adams Stokes attacks for 4 years The ventricular rate varied between 30 and 38 per minute There was no evidence of heart failure on admission to the hospital The GFR was 76 ml per minute The daily intake of sodium was progressively increased from 44 to 453 mEq The urinary excretion of sodium rose progressively to 440 mEq per day without a rise in venous pressure or any evidence of heart failure Body weight increased slightly with each increment in intake of sodium a normal response to salt loading as described by Leaf and associates[9] Since the preoperative tolerance for salt was well within the limits of normal the study was not repeated after implantation of the pacemaker

Case 2 (*Fig. 2*). A 68-year-old white man with complete heart block had had recurrent Adams-Stokes seizures for 8 years. There were no manifestations of heart failure while the patient was ambulatory. The GFR was 66 ml. per minute. While the ventricular rate was 28 to 44 per minute, the daily intake of sodium was progressively increased from 223 to 333 mEq. The urinary excretion increased correspondingly, but only to a maximum of 280 mEq. per day. At the maximum sodium intake heart failure developed, as indicated by orthopnea, pulmonary râles, a gain in weight, and a rise in venous pressure from a normal base line of 45 mm. of water to 160 mm. of water. When heart failure was evident, the intake of sodium was decreased to 44 mEq. per day. A spontaneous diuresis occurred with a loss in weight of 3.6 kilograms in 4 days. An internal cardiac pacemaker was implanted with a resultant cardiac rate of 66 per minute. After a 2-week postoperative recovery period the salt study was repeated. The GFR was 65 ml. per minute. The intake of sodium was progressively increased from 247 to 520 mEq. per day. The maximum urinary excretion of sodium reached 440 mEq. per day without evidence of heart failure. The discrepancy between intake and output was due to loss of sodium in the stools, since the patient experienced diarrhea, which necessitated termination of the study.

Case 3 (*Fig. 3*). A 62-year-old white man with complete heart block had experienced occasional Adams-Stokes attacks during the preceding 4 years. For 3 months prior to the study there was evidence of increasing congestive heart failure, indicated by dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and progressive peripheral edema. A low-salt diet, digitalis, and diuretic therapy were ineffective in controlling his symptoms while he was ambulatory. After he was admitted to the hospital, heart failure persisted while his ventricular rate with established complete heart block varied between 30 and 38 per minute. His

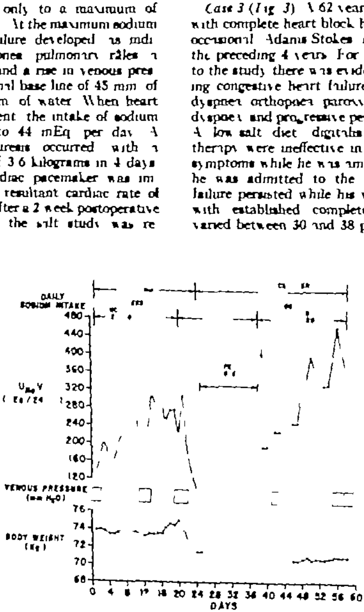


Fig. 2. Case 2, 68-year-old man. Complete heart block. No heart failure. Maximal daily excretion of sodium of 370 mEq. during bradycardia. Heart failure on daily intake of sodium up to 333 mEq. Normal maximal daily excretion of sodium (440 mEq.) and no heart failure on daily intake of sodium to 570 mEq. during cardiac pacing at 66 per minute.

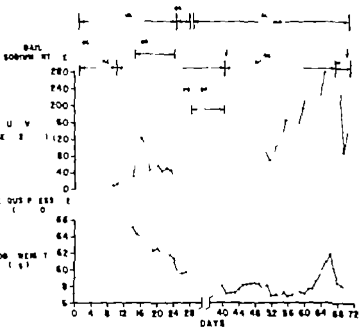


Fig. 3. Case 3, 62 year-old man. Complete heart block. Heart failure. Maximal daily excretion of sodium of 35 mEq during bradycardia. Increasing weight and venous pressure on augmenting intake of sodium to 60 mEq daily. After cardiac pacing, maximal daily excretion of sodium of 260 mEq. But gain in weight, rise in venous pressure and return of heart failure on increasing daily intake of sodium to 340 mEq.

GFR was 41 ml. per minute. His daily intake of sodium was progressively increased from 9 to 60 mEq. Concomitantly the daily excretion of sodium rose progressively but could not exceed a maximum of 35 mEq. Heart failure was intensified during this period and was associated with an increase in weight of 3 kilograms and an elevation in venous pressure from a base line of 100 mm. of water (with a rise to 135 after pressure in the right upper quadrant) to 145 mm. of water (with a rise to 200 after abdominal pressure). When a positive sodium balance became evident the intake of sodium was decreased to 9 mEq. of sodium per day. He was given 500 mg. of chlorothiazide twice daily and a moderate diuresis ensued with a maximum daily urinary excretion of sodium of 120 mEq. Retained fluid, however, was not completely eliminated until a bipolar catheter pacemaker was inserted for 3 days prior to operation.

Two weeks after an internal cardiac pacemaker yielding a ventricular rate of 66 beats per minute had been implanted the salt loading study was repeated. At this time there was no evidence of congestive heart failure. As the daily intake of sodium was increased progressively from 60 to 340 mEq. the maximum urinary excretion of sodium now reached 260 mEq. per day but at the maximum intake retention of salt and water occurred and heart failure developed as evidenced by a gain in weight of 4 kilograms, edema and rising venous pressure. The GFR was 43 ml. per minute. With a reduction in the intake of sodium to 9 mEq. per day a spontaneous diuresis ensued and the signs and symptoms of heart failure disappeared.

Case 4 (*Fig. 4*). A 68 year old woman with diabetes mellitus of many years duration and diffuse diabetic glomerulosclerosis demonstrated by renal biopsy was hospitalized because of severe congestive heart failure. Advanced or complete heart block in the presence of atrial fibrillation had been present for 2 to 3 years. Abnormal retention of fluid per

sisted despite restriction of salt, numerous diuretics and a trial of digitalis. The patient was hospitalized many times for control of the retention of fluid, which was achieved only by repeated paracenteses. The ventricular rate ranged from 44 to 48 per minute. After a bipolar catheter pacemaker had been inserted and the heart paced at 86 per minute, the urinary excretion of sodium averaged 105 mEq per day, while the intake of sodium was maintained at 43 mEq per day. During this period there was a progressive loss of body weight averaging 0.5 kilogram per day. The GFR was 26 ml per minute. When artificial pacing was discontinued, the ventricular rate reverted to 44 to 48 per minute, the urinary excretion of sodium fell to an average of 55 mEq per day, and the GFR to 19 ml per minute ($p < 0.001$). The patient gained weight at the average rate of 0.4 kilogram per day. When artificial cardiac pacing was resumed, the excretion of sodium rose promptly to 169 mEq per day and the GFR to 30 ml per minute, and there was a loss in weight of 0.6 kilogram per day.

Discussion

Heart failure was present in 2 and absent in 2 of the patients with complete or advanced heart block, although bradycardia of similar degree was present in all of them. This suggests that the bradycardia was not the sole factor in the production of heart failure, but that it was important only when there was sufficient associated cardiac or renal disease. Studies before and after an increase in the cardiac rate by a pacemaker clearly indicated that the manifestations of heart failure disappeared when the cardiac rate was increased by the artificial pacemaker.

Studies of sodium excretion with graded intakes of sodium provided a more discrete measurement of a capacity ultimately dependent on cardiac and renal function. The 4 patients who serve as the basis of this report represent a spectrum of varying capacity to excrete sodium (Table I). The first 2 patients were free of overt heart failure on admission but differed nevertheless in their maximal daily sodium excretory capacity. In the third and fourth patients with severe heart failure and im-

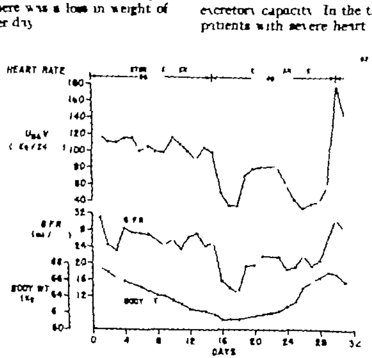


Fig. 4. Case 4. 68 year old woman. Complete or high grade heart block. Heart failure and diabetic glomerulosclerosis. On catheter pacemaker, ventricular rate of 86 per minute, heart failure diminished. Maximal daily excretion of sodium of 120 mEq. Off pacemaker, ventricular rate of 44 to 48, fall in maximal daily excretion of sodium to 55 mEq and increased weight. Rise in daily maximal daily excretion of sodium and diuresis on resuming pacemaker.

Table I. Comparative effects of idioventricular bradycardia and electrical cardiac pacing on sodium tolerance, maximal sodium excretion, glomerular filtration rate, and heart failure

Case		Heart rate (per min.)	Sodium intake (mEq./day)	Maximum sodium excretion (mEq./day)	GFR (ml./min.)	Clinical heart failure: At time of admission or prior to sodium loading	Clinical heart failure: After sodium loading
1	Pre Pacemaker	30-38	43-453	410	76	No	No
	Post Pacemaker	66					
2	Pre Pacemaker	28-44	273-333	280	66	No	Yes
	Post Pacemaker	76	47-570	410	65	No	No
3	Pre Pacemaker	30-38	9-60	35	41	Yes	Increased
	Post Pacemaker	66	60-340	260	43	No	Yes
4	Pacemaker off	44-48	100-170	55	19	Yes (severe)	
	Pacemaker on	86	43	105	26	Yes (improved)	

paired ability to excrete sodium, a difference in sodium excretory capacity was revealed by their difference in response after artificial pacing at a more rapid rate.

Patient 1, despite ventricular rates between 30 and 38 per minute, showed no manifestations of heart failure and was capable of excreting large amounts of sodium (26 Gm. of sodium chloride daily) without the development of symptoms or signs of heart failure. This suggests that no significant cardiac impairment coexisted with the bradycardia, and that the latter alone was incapable of impairing the excretion of sodium.

In Patient 2, the excretion of sodium increased up to 280 mEq. (16.5 Gm. of sodium chloride) daily. With daily intakes greater than 300 mEq., retention of sodium, gain in weight, and symptoms and signs of heart failure appeared. Since the excretory capacity of 280 mEq. of sodium represents more than the patient's usual intake of sodium, this sufficed to prevent manifestations of retention of sodium and water prior to hospitalization. But a maximal daily excretory capacity of 280 mEq. of sodium is less than normal, as indicated by his subsequent ability to excrete 400 mEq. of sodium daily when the cardiac rate was increased artificially. Progressive sodium loading may thus serve as a stress to disclose a deficiency in the excretion of sodium which indicates cardiac or renal impairment, but which is insufficient to produce overt manifestations of heart failure.

Increasing the ventricular rate by electrical stimulation improved the capacity for renal excretion of sodium in all 3 patients in whom this function was impaired (Cases 2, 3, and 4), whether or not overt heart failure was present. Patient 3, who was in refractory heart failure and retained sodium on an intake of 42 mEq. of sodium (2.5 Gm. of sodium chloride) daily when his cardiac rate was below 40 per minute, was able to remain in fluid and sodium balance on a sodium intake up to 260 mEq. (15 Gm. of sodium chloride) daily, but began to develop slight heart failure when this was increased further. This suggests that, although bradycardia was an important causative factor in the development of heart failure, since the heart failure was eliminated when the heart rate was increased, associated factors must also have contributed, since even at relatively normal cardiac rates heart failure could still be induced by high intakes of sodium which do not induce heart failure in normal persons. The relative importance

of myocardial damage as compared to intrinsic renal disease as associated factors could not be determined

Bradycardia is presumed to contribute to the development of congestive heart failure by reducing the cardiac output Cardiac catheterization studies in 6 patients with complete or 2 1 heart block but without heart failure disclosed a reduction in cardiac output although the stroke output was somewhat increased in 4 of the 6 patients[9] Stack and associates[4] found the cardiac index to be normal in a 39 year-old man with heart block but markedly diminished in 4 elderly subjects Although there was no overt evidence of clinical heart failure the right atrial and right ventricular diastolic pressures tended to be elevated and the arteriovenous oxygen difference was increased The glomerular filtration was moderately diminished and the renal blood flow greatly diminished with consequent increase in the filtration fraction as seen in congestive heart failure It was not evident how much of the hemodynamic alterations was due to the slow heart rate the aging process or arteriosclerotic heart disease Muller and Bellet[2] found that the cardiac output was reduced with heart rates of 30 to 40 per minute increased up to a critical heart rate of 50 to 65 per minute and then declined again with further increase in heart rate When heart block is produced experimentally in normal dogs there is evidence of congestive heart failure at rest or with exercise[10] which may be eliminated by increasing the cardiac rate This suggests that in dogs with experimental heart block bradycardia itself may be capable of inducing heart failure

Bradycardia with myocardial and/or renal damage in combination appear to be responsible for the production of heart failure in patients with complete heart block We were unable to differentiate the relative importance of intrinsic myocardial as compared with renal disease although the GFR correlated with capacity for sodium excretion and the presence or absence of heart failure in each of the patients During slow idioventricular rhythm the patient with the most refractory heart failure (Case 4) had the lowest GFR (19 ml per minute) the patient with less severe heart failure (Case 3) had a GFR of 41 ml per minute the patient who had developed failure only with the stress of a sodium load (Case 2) had a higher GFR of 66 ml per minute and the patient who did not develop heart failure when maximally stressed had the highest GFR (76 ml per minute) Although the method of determining endogenous creatinine clearance has many inherent errors the differences in GFR are significant and the correlation with the degree of impairment of sodium excretion indicates that a causative relationship was present

There was no perceptible change in GFR after cardiac pacing except in Case 4 This is inconclusive since the method of measurement is insensitive to relatively small changes which may nevertheless be significant Humphries and associates[4] likewise found no change in GFR and effective renal plasma flow in 2 patients with heart block (one with heart failure) when their hearts were paced at faster rates Conversely studies which we have made in dogs with experimental heart block indicate that the GFR and renal plasma flow were increased when the heart was paced at normal rates and when these renal parameters were measured by more accurate techniques[11] The difference in findings in human beings and in dogs may be due to differences in methods to species variation or to the presence of myocardial and/or renal disease in the human subjects

Conclusion

(1) Bradycardia alone does not produce congestive heart failure and may not impair maximal excretion of sodium (2) But in patients with advanced or complete heart block in whom there is impairment of sodium excretion with or without heart failure the bradycardia as well as associated factors is a significant contributory cause of these abnormalities since increased cardiac rate augments the excretion of sodium and may eliminate heart failure (3) Coexistent intrinsic myocardial and or renal disease are presumed to be the associated factors which are essential for the impairment of sodium excretion and the development of heart failure The severity of such myocardial and or renal

disease determines the degree of improvement in sodium excretion and in the clinical manifestations of heart failure after the cardiac rate has been increased with a cardiac pacemaker

Summary

1 The relative contribution of bradycardia in causing heart failure in patients with complete and advanced heart block was assessed by studying the effect of increasing the cardiac rate by an internal pacemaker

2 The ability to excrete graded loads of sodium was measured in 4 patients with complete or advanced heart block Maximal sodium excretory capacity and the presence or absence of heart failure after the stress of sodium loads during bradycardia and after increasing the cardiac rate were determined

3 One patient who had no heart failure despite cardiac rates between 30 and 40 could ingest and excrete 26 Gm of sodium chloride daily without the development of heart failure A second patient without heart failure had a maximal excretory capacity of 16 Gm daily and exhibited symptoms and signs of heart failure with intakes in excess of this quantity In the other 2 patients with heart failure at the time of hospitalization maximal daily excretory capacity for sodium was 35 to 55 mEq

4 After cardiac rates were increased to normal with an artificial pacemaker maximal excretion of sodium increased significantly In the 2 patients with heart failure at slow idioventricular rates the decompensation was eliminated or ameliorated Although the maximal excretion of sodium was increased it was still below normal in the latter 2 patients

5 The glomerular filtration rate was diminished in varied degree and correlated with the capacity for sodium excretion and the presence or absence of heart failure in each of the patients

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The effect of acute administration of chlorothiazide upon the pressor responsiveness to angiotensin and norepinephrine

*Jack G. Silak, M.D.**
*R. Ellwood Jones***
*F. A. Bashour, M.D.****
*Norman M. Kaplan, M.D.*****
Dallas, Tex.

The means by which thiazide drugs reduce blood pressure are uncertain. One possible mechanism is by decreasing the pressor responsiveness to physiologically active pressor substances. A decrease in pressor responsiveness to norepinephrine has been found after the oral administration of thiazides,[1-4] 30 minutes after intravenous infusion,[5] and during intra-arterial infusion.[6,7]

The study of Jackson and Duff[6] is the only one which examines the effect of the acute administration of chlorothiazide upon the response to norepinephrine in man. Since their finding of an impaired pressor response may have been related to the inactivation of norepinephrine by the chlorothiazide, we have examined the effect of the acute administration of chlorothiazide upon the pressor response to norepinephrine when the two agents are given in either combined or separate infusions. Similar studies were made with chlorothiazide and angiotensin, another physiologically important pressor substance.

Methods

Subjects. Studies were made on 5 healthy normotensive young men in a basal state. Studies were repeated after 2 to 14 days on 4 of the 5, with random variations in the protocol.

Infusion techniques. Infusions of 5 per cent glucose in water were begun in large antecubital veins. Blood flow was measured in the middle finger of the same hand by impedance plethysmography, and the blood pressure was recorded in the opposite forearm with a sphygmomanometer. After control values had been obtained, infusions of chlorothiazide,† norepinephrine,‡ and angiotensin§ were begun in the various

From the Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

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*Research Fellow in Medicine.
**Medical student.
***[illegible] of Internal Medicine.
****[illegible] of Internal Medicine. Address: University of Texas Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, Tex. 75235.

†Chlorothiazide (Diuril) was kindly supplied by Merck Sharp & Dohme.
‡Norepinephrine was levarterenol bitartrate (Levophed).
§Angiotensin was ... angiotensin II (Hypertensin, Ciba), kindly supplied by Dr. Jack Graham, Ciba Pharmaceuticals, Summit, N. J.

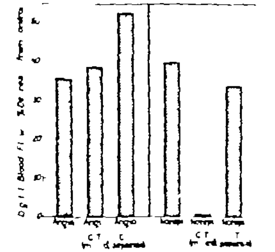


Fig. 1 Changes in digital blood flow during the infusions of angiotensin and norepinephrine alone and with chlorothiazide (C T) mixed in the same bottle and in separate bottles

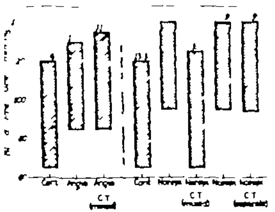


Fig. 2 Changes in blood pressure plotted as columns and digital blood flow shown as the numbers above the columns in the study on Subject C A

combinations indicated using constant infusion pumps The pressor agents were diluted in 5 per cent glucose in water angiotensin to a concentration of 0 4 μg per milliliter and norepinephrine to a concentration of 4 0 μg per milliliter The pressor agents were infused at a rate sufficient to induce a 20 mm rise in diastolic blood pressure Without a change in the rate of infusion of the pressor agent the infusion of chlorothiazide 3 mg per minute was begun In 2 studies chlorothiazide was also infused at a rate of 9 mg per minute In 6 studies the chlorothiazide was mixed with the pressor agent and the two were infused together in 8 studies the chlorothiazide was infused from a separate bottle into another antecubital vein The solutions were used within 30 minutes after preparation Each separate infusion was continued for 15 minutes The blood pressure was allowed to return to the control level before the infusion of the other pressor agent was begun

Plethysmographic technique The digital blood flow was measured with the middle finger using impedance plethysmography [19] The tetrapolar electrode system was employed with the sampling stainless steel electrodes spaced 4 cm apart The hand to which the electrodes were applied was wrapped in a cotton covering to prevent cooling and reflex vasoconstriction The hand was placed in a plane above the cardiac level Flow was allowed to stabilize for 20 to 30 minutes and then two control tracings were taken 5 minutes apart The measurements were made in the quiet at room temperature (25 C) and the body of the individual was covered in order to prevent cooling

A comparative study of blood flow in the finger using the mechanical venous occlusive plethysmograph and the electrical impedance plethysmograph has been made The measurements were made simultaneously using the middle finger of both hands one digit employed for the impedance method and the other for the occlusive method In normal subjects results with the two methods agreed r = 0 89 [20]

Results

The results of all studies were similar All are detailed in Table I the effects on digital blood flow are shown in Fig 1 and one typical study is diagrammed in Fig 2

Angiotensin Angiotensin alone in a mean dose of 10 9 mμg/Kg /min induced a 20 mm rise in diastolic blood pressure and a mean decrease in digital blood flow of 35 5 per cent from the control level (p = < 01) When chlorothiazide was infused simultaneously with angiotensin either from the same or from a separate bottle the blood pressure remained elevated and digital blood flow remained depressed with a mean decrease of 38 3

Table I Effects of angiotensin and norepinephrine upon blood pressure and digital blood flow

Subject	Pressor: Agent	Pressor: Dose (mcg/Kg/min)	Control: BP	Control: DBF	Pressor alone: BP	Pressor alone: DBF	Hydrochlorothiazide: Mixed: BP	Hydrochlorothiazide: Mixed: DBF	Hydrochlorothiazide: Separate: BP	Hydrochlorothiazide: Separate: DBF
FB	Angio	11 6	118/ 0	11 0	135/95	6 5	135/95	7 2	135/95	6 1
	Norepi	77 3	119/ 0	11 4	135/95	6 0	120/70	10 4		
LB	Norepi	82 7	130/90	9 0	150/100	6 5	135/85	9 0	155/100	6 3
	Angio	7 1	135/80	7 6	155/107	3 0	155/105	3 0	155/105	1 1
CS	Angio	12 8	1 5/75	9 7	155/95	7 7	130/90	8 0	140/90	9 2
	Norepi	178 0	170/70	10 6	138/95	8)	120/75	10 4		
CS	Norepi	128 0	120/75	13 6	148/85	8 7			145/90	9 7
	Angio	10 9	115/75	12 7	175/95	8 9			1 5/95	7 2
CA	Angio	12 5	120/65	13 6	130/85	11 4	135/85	11 1	140/97	5 9
	Norepi	123 0	120/65	13 3	140/95	5 4	175/65	13 0		
KW	Angio	4 9	115/80	7 6	130/100	1 5			130/100	2 0
	Norepi	74 4	1 0/90	3 0	135/100	1 5			140/95	2 6
KW	Norepi	4 1	115/ 0	9 8	135/90	6 8	115/70	11 0	135/90	11 0
	Angio	12 3	115/ 0	11 6	135/90	6 7	135/90	5 5		
LK	Angio	10)	105/75	13 2	170/95	3 5			120/98	7 9
	Norepi	75 0	105/75	13 8	1 5/98	7 0			17 /93	6 4
LK	Norepi	72 5	110/78	7 5	125/100	5 8	115/85	6 7		
	Angio	10 9	117/80	9 9	135/105	6 3	123/105	4 7		
Mean value with standard deviations of DBF										
	Angio	0 9 ± 1 9	118/74	10 7 ± 2 2	142/95	6 9 ± 2 9	136/75	6 6 ± 2 8	132/90	5 1 ± 2 9
	Norepi	91 0 ± 25 6	117/74	10 1 ± 3 4	136/95	6 1 ± 3 0	131/75	10 1 ± 2 1	139/93	6 7 ± 2 2

BP Blood pressure (mm Hg)

DBF Digital blood flow in ml per min per 100 ml

per cent for the mixed infusion (p = < .01) and 52.3 per cent for the separate infusions (p = < .01).

Norepinephrine. Norepinephrine alone in a mean dose of 93.0 mμ/kg./min. induced at least a 20 mm. rise in diastolic blood pressure and a mean decrease in digital blood flow of 39.6 per cent from the control level (p = < .01). When chlorothiazide was mixed with the norepinephrine in 6 studies, the pressor effect was markedly blunted, with the blood pressure falling to or near the control level and the mean digital blood flow increasing to the control level.

However, when the chlorothiazide was infused into a separate vein in the same arm at a rate of 3 or 9 mg. per minute in 8 studies, the pressor effect of norepinephrine was well maintained, and the mean digital blood flow was decreased by 33.7 per cent, significantly less than the control level (p = < .05) and almost identical to the decrease with norepinephrine alone. Chlorothiazide alone had no effect on either blood pressure or digital blood flow in these acute experiments.

Since it has been shown that norepinephrine is unstable in an alkaline medium,[1] the pH of the various solutions was determined with a Beckman pH meter. The pH of the chlorothiazide plus angiotensin and the chlorothiazide plus norepinephrine solutions was 9.0.

Discussion

The mechanism by which thiazides lower the blood pressure is unknown. At least four possibilities have been suggested: (1) a direct blocking of the pressor effect of norepinephrine[4,7,8] and angiotensin,[8] which has been observed in acute experiments; (2) a fall in blood volume, which can be shown early[3] but not after several weeks[12] when the hypotensive effect persists; (3) a decrease in total peripheral resistance,[14,15] perhaps by a direct effect on peripheral vessels related to changes in body electrolyte or water distribution;[16] and (4) a decrease in the sensitivity of cardioregulatory reflexes.[6]

Evidence supporting the first mechanism was recently reported by Jackson and Duff,[8] who studied the acute effect of chlorothiazide upon the pressor effect of norepinephrine in man. They administered the agents intra-arterially, first separately and then together (i.e., mixed in the same bottle) and measured blood flow by plethysmography. Since chlorothiazide blocked the vasoconstrictive action of norepinephrine when they were infused together, they suggested that this blockage could play an important role in the hypotensive action of chlorothiazide.

In the present study we too found a marked decrease in the pressure response to norepinephrine when chlorothiazide was added to the infusion bottle. However, when the two drugs were infused simultaneously but from separate bottles into separate veins, no such decrease in pressor responsiveness to norepinephrine was noted. The design of our study was similar to that of Jackson and Duff, with the exception that the drugs were infused intravenously and not intra-arterially.

A likely explanation for the loss of pressor effect of norepinephrine when it is admixed with chlorothiazide is the destruction of its physiologic activity by contact with the highly alkaline chlorothiazide solution. West[17] found that norepinephrine lost from 60 to 80 per cent of its pressor activity when stored for 1 hour at 37° C. at a pH of 7.9. No studies were performed with solutions that were as alkaline as the chlorothiazide plus norepinephrine solutions used by Jackson and Duff[8] and those in the present study.

No effect of the acute administration of chlorothiazide upon the pressor response to angiotensin was found. A blunting of the pressor response to angiotensin by chlorothiazide administered for 4 to 7 days has been observed[17] in a manner similar to that noted with norepinephrine. This effect is presumably related to the shrinkage of plasma volume which occurs in this time interval, since it can also be produced by deprivation of dietary sodium and can be reversed by saline infusion.[17]

These results, then, do not support the suggestion that the hypotensive effect of chlorothiazide might involve an immediate blockage of the effect of physiologically active pressor substances. One or more of the other mechanisms detailed above may be responsible for the prolonged hypotensive effect.

Summary

The effects of the acute intravenous administration of chlorothiazide upon the pressor responsiveness to norepinephrine and angiotensin II in normal human subjects have been examined by measuring blood pressure and digital blood flow. Chlorothiazide did blunt the pressor responsiveness to norepinephrine but not to angiotensin when they were administered in the same infusion. Chlorothiazide did not decrease pressor responsiveness to either agent when they were administered simultaneously but in separate infusions. The effect of chlorothiazide upon the pressor response to norepinephrine when the two are admixed is presumably related to instability of norepinephrine in the alkaline pH of the chlorothiazide solution.

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A phonocardiographic study of patients with the Starr Edwards mitral valve prosthesis

Herbert N Hultgren M D
Harold Hubis M D
Palo Alto Calif

An increasing number of patients with chronic rheumatic mitral valve disease are being treated by valve replacement employing the Starr Edwards caged ball prosthesis This valve produces loud distinctive sounds with each cardiac cycle due to impacts of the ball against the cage and the rim of the apparatus A study of the heart sounds in these patients should afford an opportunity to examine indirectly certain hemodynamic features of the cardiac cycle as well as provide information in regard to abnormal valve function In addition basic mechanisms responsible for normal heart sounds may be investigated

For these reasons a phonocardiographic study has been made of 14 patients before and after replacement of the mitral valve with a Starr Edwards prosthesis

Material and methods

The pertinent clinical data in the 14 adult patients in this study are summarized in Table I All operations were performed by Dr Norman Shumway and his associates employing a cardiopulmonary bypass technique which has been described previously [1] During the study period from March 1 1963 when the first valve replacement operation was performed to Feb 28 1964 31 mitral and aortic valve replacements have been done Fourteen patients had the aortic valve replaced and 17 had the mitral valve replaced Two patients in each group died a mortality of 13 per cent Thus the patients in this study were essentially unselected and represent an average experience with mitral valve replacement All patients underwent cardiac catheterization studies preoperatively and 6 patients have been studied in a similar manner postoperatively Phonocardiograms were recorded at a paper speed of 75 mm per second using a Sanborn Twin Beam oscillograph and the standard microphone supplied by the manufacturer Carotid and apex impulse tracings were recorded in the usual manner The duration of left ventricular systole was determined by measuring the interval from the onset of the mitral component of the first sound or the closing click of the prosthetic valve to the onset of the sound of aortic closure Left ventricular ejection time was measured from the onset of the rise of the carotid pulse to the nadir of the dicrotic notch All measurements before and after operation were made in cardiac cycles of similar duration Ejection times thus de

From the Cardiology Division and Department of Medicine Stanford University School of Medicine Palo Alto Calif
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Received for publication May 18 1964
Associate Professor of Medicine Stanford University School of Medicine Address Stanford Medical Center 300 Pasteur Dr Palo Alto Calif 94304
Fellow Cardiology Stanford University School of Medicine

termined were compared with published normal values. Analysis of the diastolic portion of the apex impulse tracing and of the filling angle was made in the manner described by Benchimol.[?] All time intervals were measured to the nearest 0.005 second as estimated with a hand lens. At least 5 consecutive measurements were made of each interval and the mean value was recorded.

Results

1 Auscultatory findings. After mitral valve replacement two loud clicking sounds with each cardiac cycle are easily heard (Fig 1). One occurs at the time of the first heart sound and has been termed the closing valve sound. The second sound occurs in early diastole, corresponds to the mitral opening snap, and has been called the opening valve sound.[?] The terms opening click (OC) and closing click (CC) might be preferable since these terms are more concise and more descriptive, even though in occasional patients the sound may not be clicking in quality. The opening click is best heard at the lower left sternal border and the closing click is usually loudest at the apex. These are the locations where the mitral opening snap and the mitral first sound are best perceived.[?] About half the patients are aware of these sounds which may also be heard in some patients with the unaided ear some distance from the chest.

2 Closing click. The closing click replaces the sound of mitral closure. It is a sound of brief duration (0.015 to 0.020 second) and usually great amplitude. An initial prominent single deflection in the phonocardiogram may be followed by one or two brief smaller deflections which occur 0.020 to 0.040 second later. The onset of the closing click occurred from 0.06 to 0.08 second after the QRS onset with a mean value of 0.073 second (Figs 1 and 2). This is a slightly longer interval than has been observed in normal subjects.[?] In most patients the Q-CC interval was less than the preoperative Q-1 interval (Fig 2).

In all patients in whom atrial fibrillation persisted after the operation the Q-CC

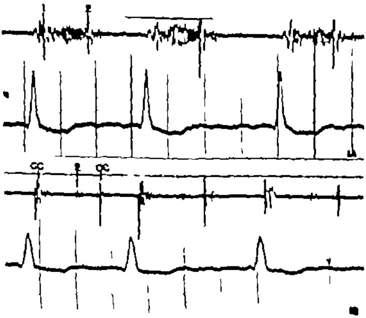


Fig 1 Apical phonocardiograms of a patient with mitral insufficiency and a loud musical apical systolic murmur before and after prosthetic valve replacement (Patient 8, J. K.). 1 First sound. 2 Second sound. CC Closing click of prosthetic valve. OC Opening click of prosthetic valve. In this and subsequent tracings faint sound deflections have been slightly retouched.

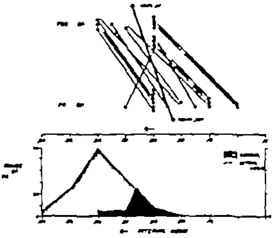


Fig 2 Q M and Q CC intervals before and after mitral valve replacement Observed Q M intervals in normal subjects and patients with mitral stenosis in lower panel from Craige

interval varied inversely with the duration of the preceding R R interval (Fig 3)

A characteristic feature of the first heart sound in patients with atrial fibrillation is a variable loudness related inversely to the preceding R R interval (Fig 4) This phenomenon is seen in patients with out valvular disease and in patients with mitral insufficiency but not in patients with dominant mitral stenosis[7] In 4 patients with atrial fibrillation the loudness of the closing click bore a similar inverse relationship to the preceding R R interval (Fig 5) A striking decrease in loudness of the closing click occurred with R R intervals of 1 0 second or longer This can easily be detected by auscultation

3 *Tricuspid closure sound* Sounds of tricuspid closure were identified in all patients before and after operation No changes in timing were noted after the operation The sounds occurred from 0 04 to 0 06 second after the QRS onset and from 0 02 to 0 04 second after the initial ventricular motion in the apex impulse tracing They always preceded the closing click The sounds varied in intensity in relation to the preceding R R interval in the expected manner[8]

4 *Systolic ejection sounds* Systolic ejection sounds were clearly identified in 3 patients prior to operation Postoperatively ejection sounds were identified in 12 patients and were probably present in the other 2 The sounds were best recorded at the left sternal border or base and began 0 12 to 0 15 second after onset of the QRS (Fig 6) It was not possible to determine whether the ejection sounds were of pulmonary or aortic origin An aortic origin was suggested in some patients who had clinical evidence of mild aortic valve disease A prosthetic origin cannot be excluded

5 *Systolic murmurs* Systolic murmurs of mitral origin disappeared after valve replacement An example is Patient 8 (J K) who prior to operation had a Grade 5 6 *full musical systolic murmur* at the apex with a palpable thrill A severe degree of mitral insufficiency and left ventricular failure were demonstrated by cardiac catheterization After valve replacement the murmur was no longer present (Fig 1) Murmurs of mitral origin were noted in only 1 patient (Case 13 J I) after replacement of the mitral valve As might be expected murmurs of aortic origin were not affected

6 *Splitting of the second sound* No patient exhibited paradoxical splitting prior to operation Aortic closure preceded pulmonary closure by a mean interval of 0 04 second This was not significantly altered by operation except in Patient 7 (I I) in whom the splitting increased from 0 04 to 0 08 second This was due to a right bundle branch block which developed

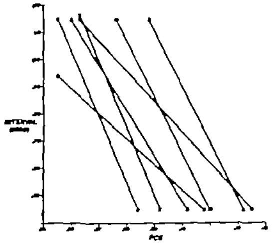


Fig 3 Relationship between the Q-opening click interval and the preceding R R interval in 7 patients with prosthetic mitral valve replacement

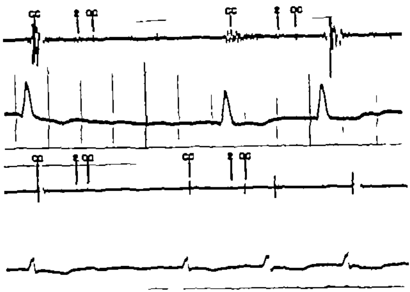


Fig 4 Apical phonocardiograms of 2 patients with prosthetic mitral valve replacement showing faint sounds following long R R interval *Top* Patient 8 (J K) *Bottom* Patient 10 (R B)

during operation and persisted The mean interval between aortic and pulmonary closure after operation was 0 043 second

7 Duration of left ventricular systole The interval from the onset of the mitral first sound to the onset of the aortic closure sound was 0 272 second at a heart rate of 75 prior to operation This interval was 0 276 second after operation and both values are normal

8 Systolic ejection time All values were normal before and after valve replacement

9 Apex impulse tracings Apex impulse tracings provided further evidence of the slight delay of the closing click The interval from the onset of precordial systolic motion to the onset of the click was 0 05 second as compared to a normal value of 0 01 second [9] Filling angles were increased postoperatively in patients with dominant mitral stenosis and were decreased in patients with dominant mitral insufficiency The mean postoperative filling angle was 53 5 degrees which is in the normal range of 32 to 77 degrees reported by Benchimol [9]

Rapid inward deflections were not seen with early diastolic sound Such deflections are commonly observed in association with gallop sounds in patients with valvular disease [10,11]

Aside from these deviations the form of the apex impulse tracing did not differ in general countour and appearance from that seen in normal subjects [9]

10 Opening click of the prosthetic valve The opening click like the closing click had a brief duration of 0 010 to 0 015 second (Figs 1 and 5) In most tracings the initial loud brief component was followed closely by a second or third faint sound producing a total duration of 0 04

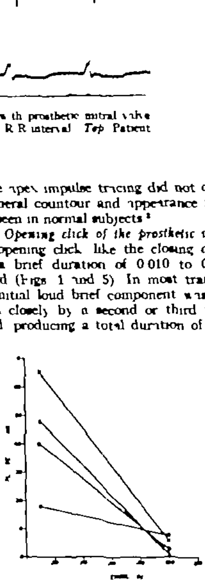


Fig 5 Relationship between loudness of the closing click and the preceding R R interval in 4 patients with atrial fibrillation and prosthetic mitral valve replacement

to 0.05 second. The opening click occurred from 0.07 to 0.15 second (mean of 0.110 second) after the onset of aortic closure (Fig. 6). In 6 patients with opening snaps prior to operation the A₂-OS interval varied from 0.06 to 0.10 second (mean of 0.086 second) (Fig. 7). In 5 patients with atrial fibrillation no relationship could be demonstrated between the length of the preceding R-R interval and the A₂-OC interval. In 2 patients the interval varied in the expected manner (Fig. 8).

The time relationship between the opening click and the apex impulse tracing was found to be similar to that of the opening snap in mitral stenosis. The click occurred at the nadir of the early diastolic portion of the rapid filling curve. The opening click never occurred at the end of the rapid filling curve, where the third heart

Table I. *Summary of phonocardiographic findings before and after mitral valve replacement in 14*

Patient	Age (yr) Sex	Lesion	Rhythm		Q–M (sec)	Q–CC (sec)	Tricuspid sound		Ejection sound		A_2–OS (sec)	A_2–OC (sec)
			Preop	Postop			Preop	Postop	Preop	Postop		
R B	54 M	MS	AF	AF	0 11	0 08	+	+	+	+	0 09	0 12
J B	41 F	MI	AF	AF S	0 09	0 08 0 05	+	+	+	+	0 10	0 11
D M	33 F	MS	S	S	0 10	0 07	+	+	+	+	0 06	0 08
F C	35 F	MS MI	AF S	AF	0 08	0 06	+	+	+	+	0 08	0 11
J M	34 M	MS MI	S AF	AF	0 08	0 06	+	+	+	+	0	0 07
K F	54 F	MS MI	AF	AF	0 08	0 06	+	+	+	+	0 07	0 10
[illegible]	27 M	MI	S	S	0 08	0 08	+	+	+	+	0	0 08
J K	56 M	MI	AF	AF	0 08	0 08	+	+	+	+	0	0 12
L A	39 F	MI	AF	AF	0 08	0 08	+	+	+	+	0 07	0 16
R B	57 F	MS MI	S	S AF S	0 07	0 08 0 05	+	+	+	+	0 08	0 11
V B	40 F	MI	S	S	0 08	0 08	+	+	+	+	0 10	0 15
R H	34 M	MS	AF	AF	0 09	0 08	+	+	+	+	0 07	0 10
J F	40 M	MS MI	AF	AF	0 11	0 09	+	+	+	+	0 04	0 075
L R	61 F	MS MI	AF	AF	0 08	0 07	+	+	+	+	0 08	0 13
Mean	44 1/2				0 087	0 073					0 086	0 110

MS, Mitral stenosis; *MI*, Mitral insufficiency; *AF*, Atrial fibrillation; *S*, [illegible] rhythm; *M*, Mitral [illegible] of the first heart [illegible] *CC*, Closing [illegible] the nadir of the early diastolic portion of the apex impulse tracing to the opening snap or opening click. A [illegible] indicates that the [illegible] rhythm. A zero (0) means [illegible] absence of the phase [illegible]. A blank space indicates that adequate data were [illegible] available. *CI* [illegible]

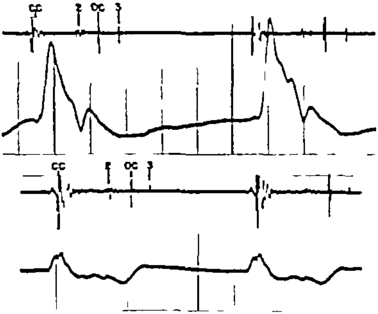
sound is usually seen The mean interval from the nadir to the opening click was 0 020 second (Table I) The timing of the opening click and the mitral opening snap in relationship to the apex impulse is illustrated in Figs 7 9 and 11

II Extra early diastolic sounds (prosthetic third heart sounds) In 11 of 14 patients an extra diastolic sound followed the opening click by a constant interval of from 0 04 to 0 13 second (mean of 0 08 second) The mean A_2 sound interval was 0 18 second In some patients the sound was nearly as loud as the opening click It had a similar brief duration The sound occurred at the end of the rapid filling angle of the apex impulse tracing where third heart sounds and protodiastolic gallops occur (Table II) Unlike such sounds the extra sound produced no simultaneous de

patients

Third sound	Prosthetic third sound	Presystolic gallop sound	Prosthetic atrial sound	Nadir to OS (sec)	Nadir to OC (sec)	Filling angle		Size of Starr valve	Preop MVA (cm)	PA wedge resting	Mean PA pressure	CI (L /min M)
						Preop	Postop					
+	+	0	0	0 04	0 03	4?	58	2M	1 0	14		? 3
0	+	0	0		0 03		47	3M	2 5	19	33	1 8
0	+	0	+	0 00	0 00			?M	9	22	32	1 8
+	+	0	F+ L+	0 00	0 06	38	21	2M	1 5	2?	29	2 0
+	+	0	0		0 05		55	2M	1 0	16	33	2 2
+	+	0	0	0 00	0 00	16	56	2M	8	24	35	2 2
+	+	+	F+ I+		0 00	50	31	3M	Severe MI	14	24	2 9
0	+	0	0		0 03		53	3M	Severe MI	26	30	1 6
+	0	0	0	0 00	0 05	71	60	3M	Severe MI	18		1 7
+	0	0	E+ I+	0 00	0 03	58	6?	2M	0 8	21	38	2 2
+	+	+	E+ L+	0 01	0 03	66	45	3M	Severe MI	?4	27	2 5
0	+	0	0	0 00	0 00	75	6	2M	0 7	14	45	1 6
+	0	0	0	0 00	0 00	62	70	M	0 8	33	66	1 9
+	+	0	0	−0 0?	0 00	74	64	3M	2 0	18	?	2 6
				0 003	0 00	54	53?			?0 4	34 4	2 1

[illegible] OS Opening snap of the mitral valve OC Opening click of the prosthesis [illegible] OS OC Interval [illegible] E Early [illegible] L Late [illegible] Direct left atrial pressure [illegible]



F 9 I ostoperative phonocard ogram in Patient (J B) bowing relat on hip of prosthet c alve sound to the carotid pulse (above) and the apex impulse tracing (below) Note the tricu pid sound preceding the CC and the ejection sound immediately followin the CC A prosthetic third sound present in the lower tracing

deflection of the apex impulse tracing (Figs 6 d 9)

b I Sounds related to atrial systole In 4 5 patients with sinus rhythm two sounds related to atrial systole were identified (Figs 10 and 11) A faint sound occurred from 0 06 to 0 11 second (mean of 0 095 second) after the onset of the P wave It was synchronous with the onset of the atrial deflection in the apex impulse trac ing A louder later sound occurred from 0 12 second to 0 18 second (mean of 0 16 second) after the onset of the P wave This sound coincided with the peak of the atrial deflection in the apex impulse trac ing (Fig 11) The time relationship of the sounds related to atrial systole are sum marized in Table III

Discussion

The closing click of the prosthetic valve is analogous to the mitral component of the first heart sound At valve replace ment, the Q-closing cli erval is de creased as compared to operative Q 1 interval but still slightly prolonged (mean of 0 073 as com pared to normal values)

Four factors may be responsible for this slight delay

1 A small pressure gradient may be present across the prosthesis Diastolic gradients across the Starr Edwards valve measured during catheterization of the left side of the heart have been reported[10] This gradient becomes greater with short R R intervals and would result in the greater delay of the closing click under these conditions This is probably the most important factor responsible for the prolonged Q CC interval

2 The position of the ball in the cage may influence the loudness of the closing click After long R R interval the ball may move toward a closing position and thus when ventricular systole occurs the distance it moves is less and the sound produced is faint The relationship between the loudness of the closing click and the R R interval supports this viewpoint

3 Atrial fibrillation alone may result in a light prolongation of the Q CC in terval This may be due to the effect of atrial systole producing a closing move ment of the ball just as atrial systole to produce a closing movement of

the normal mitral valve.[4,14] Two patients in this series suggested that a similar phenomenon occurs with the Starr Edwards prosthesis. In Patient 10 (R.B.) atrial fibrillation appeared 8 days after valve replacement. The Q-CC interval was 0.08 second at a heart rate of 85 per minute. Sinus rhythm was re-established with a small amount of quinidine. The Q-CC interval was now 0.05 second at the same heart rate. A similar phenomenon was present in Patient 2 (J.B.). After valve replacement, when atrial fibrillation persisted, the Q-CC interval was 0.085 second at a rate of 70. After sinus rhythm had been established, the Q-CC interval was 0.055 second at the same heart rate. A similar relationship was found many years ago by Cossio[14] in patients without mitral valve prosthesis.

Atrial fibrillation alone is probably not an important determinant of the Q-CC interval since there was only a slight difference in the Q-CC interval between patients with atrial fibrillation (0.075 second) and those with sinus rhythm (0.066 second) after valve replacement.[4]

4. Finally, the loss of papillary muscle function may result in slight prolongation of the Q-CC interval. Some workers believe that contraction of papillary muscles during early isometric contraction facilitates closure of the mitral valve.[7]

The loudness of the closing click was variable in patients with atrial fibrillation and this variation was related inversely to the duration of the preceding R-R interval. Similar observations have been made in normal subjects and in patients with mitral insufficiency, but not in patients with dominant mitral stenosis.[7,14] Variation in the position of the mitral valve leaflets at the time of onset of left ventricular systole is thought to be the cause of the variation.[14] The predictable variations seen in patients with prosthetic valves suggests that the position of the ball at the time of onset of left ventricular systole determines the loudness of the closing click. Very faint sounds noted after long R-R intervals suggest that the ball may be very near to a closed position at the onset of ventricular systole. Conversely, loud sounds would be produced if the ball were in the cage at the onset of systole, thus allowing a greater travel distance and a resultant louder sound of impact. The velocity of initial rise in pressure in the left ventricle may also influence the loudness of the closing click. This factor has not been assessed in this study. The velocity of rise in pressure is influenced both by heart rate and the degree of left

Table II. Summary of data on prosthetic third heart sounds in 11 patients with mitral valve replacement

Patient		OC-3	A-3	Loudness OC/3	Angle to 3
1	R.B.	0.06	0.18	10/4	0.02
2	J.B.	0.12	0.24	13/5	0.04
3	D.M.	0.08	0.16	12/6	
4	F.C.	0.04	0.16	15/11	
5	J.M.	0.09	0.18	14/2	0.00
6	K.F.	0.08	0.16	22/11	−0.04
7	[illegible]	0.13	0.21	14/3	−0.02
8	J.K.	0.07	0.19	13/3	0.00
9	V.B.	0.07	0.19	20/2	
10	R.H.	0.07	0.13	22/4	
11	L.P.	0.08	0.174	13/3	−0.04
Mean		0.08	0.18	15/5	−0.006

OC-3: Interval [illegible] opening click [illegible] onset of the third [illegible] A-3: Interval from aortic closure [illegible] onset of sound. Loudness of the sound [illegible] expressed as [illegible] of the deflection [illegible] made by [illegible] [illegible] end of the [illegible] [illegible] the [illegible] [illegible]

Table III. Time relationships of sounds following atrial systole in 4 patients with mitral valve replacement

Patient	P-A (sec.)	P-4 (sec.)	Onset of a wave to 4 (sec.)	Onset of a wave to 4 (sec.)
10	0.11	0.17	0.00	0.06
11	0.09	0.17	0.00	0.07
4	0.06	0.12	0.00	0.07
7	0.12	0.18	0.00	0.06
Mean	0.09	0.16	0.00	0.065

P-A [illegible] P-4: Intervals from the onset of the P wave to the onset of the [illegible] and [illegible] atrial sounds. The [illegible] of the [illegible] determined by the apex impulse tracing.

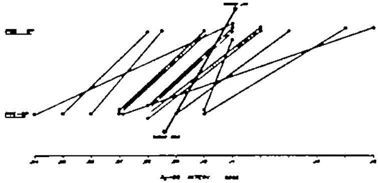


Fig. 7. Relationship between the A–OS interval and the A–OC interval before and after prosthetic mitral valve replacement.

ventricular filling. High velocities occur with rapid heart rates and also with greater degrees of left ventricular filling, so that the final effect of both these factors in an individual patient cannot be predicted.

Ejection sounds may contribute to the first heart sound not only in normal subjects but also in patients with mitral valve disease. In the latter instance the ejection sound may be difficult to identify since the sound of mitral closure is delayed and fusion of the two sounds may occur. After prosthetic valve replacement, ejection sounds are more easily identified for two reasons: (a) delay of the closing click is slight, and (b) the closing click has a brief duration. Probably for these reasons ejection sounds were noted in all patients although they were identified preoperatively in only 2. These data suggest, therefore, that systolic ejection sounds of aortic or pulmonary origin may be frequent in mitral valve disease and may be an important part of the first heart sound in such cases.

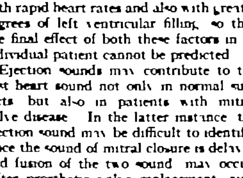


Fig. 8. Relationship between the A–OC interval and the preceding R-R interval in 2 patients after mitral valve replacement. Numbers in parentheses refer to patient numbers in Table I.

The opening click of the prosthetic valve is produced by impact of the ball against the cage as the left ventricular pressure falls below the left atrial pressure. It corresponds hemodynamically to the mitral opening snap. The A–opening click interval of 0.110 second is compatible with only a slight elevation of left atrial pressure, which has been confirmed by hemodynamic studies.[12] Application of the Wells index to the mean values of 0.073 second for the Q-CC interval and 0.111 second for the A-OC interval in this study results in a calculated mitral valve orifice area of 2.5 cm. This value corresponds to the mitral valve area calculated in 5 patients in this series determined by postoperative hemodynamic studies and observations of other workers.[12] It is similar to the hydraulic area of Starr-Edwards valves predicted by studies made in an artificial perfusion system.[1]

Zitnik and Burchell[4] noted that the A–OC interval varied inversely with the length of the preceding R-R interval in 1 of their 6 patients. In this study a similar relationship was noted in only 2 of 5 patients. In the 4 patients in whom the relationship was not observed, ventricular irregularity was sufficient to allow a wide range of R-R intervals to be studied. This lack of variation in the A–OC interval is compatible with the small degree of obstruction produced by the prosthetic valve.

Apex impulse tracings were essentially similar in form to records obtained in

normal subjects Diastolic filling angles were normal The relationship of the prosthetic opening click to the nadir of the early diastolic portion of the apex impulse was similar to that in mitral stenosis In neither situation was there a constant relationship between these two phenomena

Of particular interest is the early diastolic sound which follows the prosthetic opening click The sound corresponds in timing and in relationship to the apex impulse to the normal third heart sound or to the proto diastolic gallop sound It is possible that these sounds have a common hemodynamic basis and are related to a transient reversal of the atrioventricular pressure gradient at the time of rapid ventricular filling This would cause the ball to move out of the cage striking the ring and making a sound analogous to the closing click Such reversed pressure gradients in patients without prosthetic valves have been demonstrated Crevasse and his workers however could not demonstrate reversal of the atrioventricular pressure gradient at the time of presystolic and protodiastolic gallop sounds in dogs or patients Preliminary cineangiographic studies in our laboratory have demonstrated a more likely mechanism of the early diastolic sounds Initial diastolic motion of the left ventricle is rapid and consists of a downward motion of the apex and a simultaneous upward motion of the mitral annulus and the prosthesis This upward motion of the annulus is abruptly checked The ball by the inertia imparted to it by the upward movement of the prosthesis continues to move until its movement is checked by

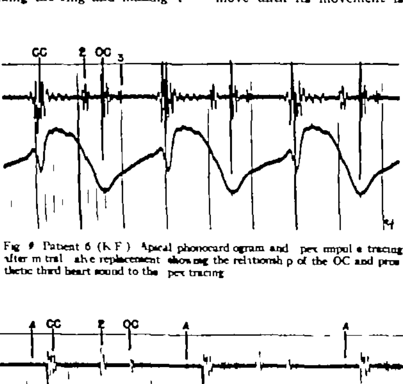


Fig 9 Patient 6 (K F) Apical phonocardiogram and apex impulse tracing after mitral valve replacement showing the relationship of the OC and prosthetic third heart sound to the apex tracing

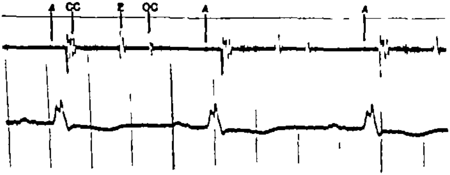


Fig 10 Patient 11 (V B) An atrial sound precedes the CC and follows the onset of the P wave by 0 17 second A prosthetic third heart sound is also present

the rim of the prosthesis thus producing the sound. Thus in analyzing the sounds produced by the prosthesis one should consider not only the effect of pressure gradients affecting the motion of the ball but also movements of the prosthesis which may affect the relative position of the ball in the cage. Sudden acceleration or deceleration of the prosthesis may impart velocity to the ball causing it to strike the rim or the cage and thus produce sounds that are independent of atrio

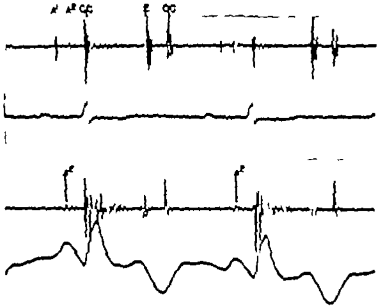


Fig. *11*. Patient 10 (R.B.). The [illegible] sound follows atrial systole and precedes the CC. In the lower panel the late atrial sound occurs at the peak of the atrial deflection of the apex impulse tracing.

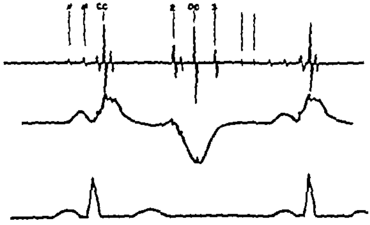


Fig. *12*. Composite apical phonocardiogram, apex impulse tracing and electrocardiogram showing the time relationships of the sounds described in this paper. A^1 and A^2 are atrial sounds. A tricuspid sound precedes and an ejection sound follows the closing click. The second sound ( ) demonstrates aortic and pulmonary components in their usual relationship. A prosthetic third sound follows the opening click. Random diastolic clicking sounds are present (x).

ventricular pressure gradients The analogy of dice being shaken in a box is applicable to this concept

Transient inward motion of the precordium at the time of the diastolic sound was not observed in any of the patients in this series Such deflections are commonly seen in apex tracings of normal subjects with third heart sounds or patients with early diastolic gallop sounds It has been suggested that this transient motion is due to the jerk of the chordae as the mitral valve is displaced toward the atrium [18,17] Absence of this deflection in the patients in this study in whom the chordae had been removed would support this hypothesis

The origin of the late atrial sound may be similar to that of the early diastolic sound With atrial systole the mitral annulus and the prosthesis may move toward the atrium If this motion is suddenly checked the ball by virtue of its inertia may strike the rim of the prosthesis and produce a sound Presumably it again moves toward the cage before the onset of atrial systole Transient reversal of the atrioventricular pressure gradient during rapid ventricular filling may cause the ball to move toward the rim as well Such a reversal of pressure may initiate the closing movement of the normal or diseased mitral valve [18,23,27] Such reversals of the pressure gradient were however not observed by Crevasse and his workers [24]

Considering the fact that the prosthetic valve offers definite obstruction to ventricular filling it seems unlikely that filling would therefore be rapid enough to produce a reversal of the pressure gradient between the left atrium and the left ventricle if indeed this phenomenon ever occurs Tensing of the chordae due to annular descent as described by Nixon [27] seems unlikely because of the removal of most of the chordae and papillary muscles by the operation Because of their timing and probable similar mechanism of production such sounds could be called prosthetic third and prosthetic fourth heart sounds

The initial atrial sound occurs at the onset of atrial contraction This sound could be produced by the ball being moved into the cage by the initial portion of atrial systole if the ball had moved slightly away from the cage prior to atrial contraction

The two sounds which follow atrial systole correspond closely in timing to similar atrial sounds studied by Weitzman [28] He noted an early inaudible atrial sound occurring 0 09 second (range of 0 08 to 0 10 second) after onset of the P wave and a later louder sound occurring 0 12 second (range of 0 09 to 0 16 second) after the P wave He attributed the earlier sound to actual muscular contraction of the auricle and the later sound was described as a filling sound produced by blood entering the ventricle from auricular systole

Additional studies of simultaneous pressures in the left atrium and left ventricle as well as cineangiographic study of the movements of radiopaque ball prostheses will be necessary to confirm these hypotheses further Such studies are currently being conducted in our laboratory

These studies describe the phonocardiographic features of patients with essentially normal prosthetic valve function Abnormal valve function would be expected to produce several characteristic changes Mitral insufficiency usually due to a partial separation of the suture line will produce an apical systolic regurgitant murmur A valve that is too small or partially obstructed would result in a greater delay in the Q CC interval and a shortening of the A_2 OC interval These changes were partly illustrated by Patient 13 (J F) At the time of follow up study a Grade 3/6 full systolic murmur was present at the posterior axillary line in the sixth intercostal space The Q CC interval was prolonged (0 09 second) the Q OC interval was short (0 075 second) and the latter interval varied predictably with the duration of the preceding R R interval (Fig 8) Cardiac catheterization study demonstrated hemodynamic improvement after operation but the pulmonary artery wedge pressure was 23 mm Hg and the pressure curve contour was compatible with mitral insufficiency Re operation has been scheduled

Fig 12 is a summary diagram of the sounds following mitral valve replacement which are described in this paper

Summary

1 Phonocardiographic studies have been performed in 14 patients who have had complete mitral valve replacement with the Starr Edwards caged ball prosthesis

2 Two prominent sounds occur with each cardiac cycle—the prosthetic closing click (CC) and the prosthetic opening click (OC) The sounds correspond to mitral closure and the mitral opening snap in their relation to the cardiac cycle

3 A mean Q CC interval of 0 073 second and an A₂-OC interval of 0 110 second indicate the presence of only mild obstruction by the prosthetic valve with an estimated mean effective valve area of 2 5 cm

4 Variation of the Q CC interval the loudness of the CC and the A₂-OC interval has been examined in atrial fibrillation

5 An early diastolic sound (prosthetic third heart sound) has been recorded in 11 patients (79 per cent) It occurs approximately at the time of the normal third heart sound in relation to the cardiac cycle and the apex impulse

6 Sounds related to atrial systole (prosthetic atrial sounds) have been observed in 4 of 5 patients with sinus rhythm An early sound occurs 0 095 second and a late sound occurs 0 16 second after the onset of the P wave Prosthetic third sounds and late prosthetic atrial sounds appear to be produced by movements of the prosthetic valve and mitral annulus during atrial systole and early diastolic ventricular filling

7 Phonocardiograms of patients with the Starr Edwards mitral prosthesis may give indirect information about residual hemodynamic abnormalities and valvular malfunction

Addendum

Since this paper was submitted for publication a total of 45 patients have had mitral valve replacements at the Stanford Medical Center with an unchanged mortality rate Twenty nine have undergone complete phonocardiographic studies The results in the entire group are similar to those in the first 14 patients reported on in this paper The mean Q CC interval was 0 076 second The mean A_2-OC interval was 0 113 second Prosthetic third heart sounds were recorded in 18 patients (62 per cent) The mean A_2 prosthetic third sound interval was 0 183 second Early prosthetic atrial sounds were recorded in 6 of 9 patients with sinus rhythm The mean interval from the onset of the P wave to the sound was 0 105 second Late prosthetic atrial sounds were recorded in 8 patients The mean P-late atrial sound interval was 0 155 second Variation in the A_2 OC interval was noted in only 4 of 19 patients with atrial fibrillation

A second operation has been performed in Patient 13 (J F) Partial disruption of the valve suture line had occurred permitting moderate mitral insufficiency This was corrected and the patient s postoperative course was uneventful The Q CC interval remains unchanged (0 09 second) but the Q OC interval is now longer (0 11 second) but with similar variation in this interval with variable diastolic filling periods

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A study of ventricular septal defect associated with aortic insufficiency

*Katherine H. Halloran, M.D.**
Norman S. Talner, M.D.
Marie J. Browne, M.D.
New Haven, Conn.

Although recent reports have emphasized the clinical and pathologic features of a ventricular septal defect associated with aortic insufficiency, the natural history of this complex is not completely clear.[1] Since aortic insufficiency may become more significant over a period of years, it is of importance from the surgical standpoint to establish the time of onset of the regurgitation and to evaluate any changes in the magnitude of regurgitation as these patients are observed. This communication presents the course of 12 patients with a ventricular septal defect and aortic insufficiency who were followed for a period of 5 years or longer, 8 of whom underwent open heart surgery.

Clinical data (*Table I*). Twelve patients with a ventricular septal defect and aortic insufficiency were seen at the Pediatric Cardiac Clinic of the Grace-New Haven Community Hospital from January, 1949, through December, 1963. Seven were females and 5 were males. The age at first visit ranged from 2 months to 11 years. Six patients were first seen before 16 months of age. The patients were followed over a period of 5 to 13 years, 7 into adolescence. Eight patients underwent open heart surgery, 5 during adolescence, 1 at 10 years, and 2 at 8 years of age.

The children were referred to the clinic because of a heart murmur. Six of the older children also had easy fatigability and mild dyspnea with exercise. Frequent respiratory infections, cyanosis, and signs of congestive failure were never noted. Five were below the third percentile in weight and height, whereas 3 were at the tenth percentile. The other 4 patients were in the fiftieth percentile or greater.

In all but one patient, physical examination revealed a loud pansystolic murmur which was harsh, Grade 3-4/6 in intensity, heard maximally along the lower left sternal border. This was always accompanied by a systolic thrill in the same area. There was no precordial heave or chest deformity. In 1 patient (D. W.), in whom a ventricular septal defect was demonstrable only by intracardiac phonocardiography, the murmur was Grade 2 in intensity and very high pitched.

The diastolic murmur of aortic insufficiency was ultimately heard along the mid left sternal border in all patients and was described as a high pitched, decrescendo blow. Evaluation of the age of the

From the Department of Pediatrics, Yale University School of Medicine, and the Pediatric Service, Grace-New Haven Community Hospital, New Haven, Conn.
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*Address: Department of Pediatrics, Yale University School of Medicine, 333 Cedar St., New Haven, Conn. 06504.

patients at the time of appearance of this murmur was made in an attempt to estimate the onset of regurgitation. Of 7 patients in whom the age of onset of the diastolic murmur was known, the range was from $2\frac{1}{2}$ to 9 years, with a median age of 6 years. These children had been followed in the clinic for $1\frac{1}{2}$ to 8 years before this murmur was heard. A diastolic murmur was first heard at the age of 6 months in one infant who also had a presumed small patent ductus ligated at 18 months. After ligation, the diastolic murmur persisted unchanged. The other 4 patients were noted to have a diastolic murmur at the time of the first visit, and all of these children were 4 years of age or older. The systolic murmur combined with the diastolic murmur had a to and fro rather than a continuous quality.

A pulse pressure of 60 mm. Hg or greater was noted in 9 of the 12 patients and was usually accompanied by bounding femoral pulsations with a Duroziez murmur. Patients with a pulse pressure greater than 60 mm. Hg had evidence of cardiac hyper

Table I. Clinical data

Patient	Age at first visit	Systolic murmur (grade)	Diastolic murmur first noted	BP (mm. Hg)	Growth percentile		Fatigability	Chest x-ray findings	Surgical findings
					Height	Weight			
R A	1 mo	3 harsh	$3\frac{1}{2}$ yr	94/50	10th	10th	0	LVE large aorta	0
R S	1 mo	3 harsh	6 mo	100/40	3rd	3rd	+	LVE RVE large aorta	PDA (18 mo) small VSD AI (8 yr)
S E	2 mo	3 harsh	6 y	100/30	25th	50th	0	LVE large aorta	VSD small AI
D B	3 mo	3 harsh	4 yr	110/40	3rd	3rd	0	Moderate LVE RVE	0
R G	5 mo	4 harsh	9 y	110/80	10th		0	Slight EH	VSD AI left cusp
A Z	13 mo	3 harsh	$2\frac{1}{2}$ yr	130/70†	10th	3rd	+	Slight EH with RVE	Small VSD AI acoronary cusp
H K	28 mo	4 harsh	7 yr	105/40†	10th	75th	+	LVE large aorta	0
T S	$4\frac{1}{2}$ yr	4 harsh	$4\frac{1}{2}$ yr	110/30	3rd	3rd	0	Marked LVE progressive aortic enlargement	Small VSD AI acoronary cusp‡
D S	$4\frac{1}{2}$ y	3 harsh	6 yr	140/70†	30th	50th	+	Slightly increased pulmonary vasculature no EH normal aorta	Small VSD AI right cusp
D P	6 yr	4 harsh	6 y	130/30	30th	50th	0	Moderate EH large aorta	Small PDA ( ) (8 y) small VSD ruptured sinus of Valsalva AI (17 yr)
E M	8 yr	3 harsh	8 y	110/40	3rd	3rd		LVE large aorta	Small VSD AI acoronary cusp
J J	11 yr	3 harsh	11 y	140/60	50th	50th	+	Borderline EH	Thoracotomy PDA§

*Blood pressures obtained after the diastolic murmur was noted.
†Increase in pulse pressure with appearance of diastolic murmur.
‡Died 24 hr postoperatively [illegible]
§[illegible]
EH: Enlarged heart. LVE: Left ventricular enlargement. RVE: Right ventricular enlargement. PDA: Patent ductus arteriosus. VSD: Ventricular septal defect. AI: Aortic insufficiency.

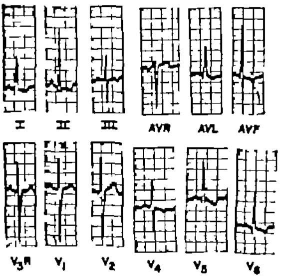


Fig 1 Electrocardiogram of Patient E M Precordial Lead V V and V at one half standardization Left ventricular hypertrophy with T wave inversion in Leads I II V1 V and V and minimal S T segment depression

trophy on the electrocardiogram and x ray film Two of the patients with a normal pulse pressure (S E R C) were noted also to have left ventricular hypertrophy by electrocardiogram and x ray film The pulse pressure was never increased in these 2 patients although aortic insufficiency was present at the time of operation Of the 7 patients who developed a diastolic murmur while under observation 4 concomitantly developed widened pulse pressures

A mid-diastolic apical flow murmur was heard in 6 patients despite the fact that the pulmonary flow as estimated at catheterization was less than two times systemic flow

Electrocardiographic findings (Table II) The salient electrocardiographic data prior to operation are given in Table II The electrical axis was in the normal range for all varying from 45 to 90 degrees An interpretation of left ventricular hypertrophy according to the criteria recommended by Nadas was made in 7 patients based in 5 on increased voltage of the R wave in left precordial leads with S T segment or T wave abnormalities and in 2 patients only on markedly increased voltage in S_{V1} and R_{V6} (Figs 1 and 2)

In 3 patients the precordial voltage was suggestive but not diagnostic of left ventricular hypertrophy The electrocardiogram was normal in all respects in 2 patients Electrocardiographic evidence of progressive left ventricular hypertrophy was noted in 2 patients one of whom also showed progressive cardiac enlargement and aortic dilatation on the x ray films The electrocardiographic interpretation was consistent with the x ray findings except in 1 patient (R S) in whom the electrocardiogram was normal despite a markedly enlarged heart on x ray examination

X ray findings The pertinent x ray findings are as follows The over all heart size as estimated by chest x ray films was normal in 5 patients slightly to moderately increased in 6 and markedly increased in 1 Enlargement was left ventricular in 7 of the 12 although 3 showed some evidence of biventricular enlargement Marked left ventricular enlargement with progressive dilatation of the aorta was observed in 1 patient (T S) during the period from age 4 years to age 10 (Fig 3) In 1 other patient (E M) progressive left ventricular enlargement and aortic dilatation was noted over a 1 year period A prominent ascending aorta was apparent in 4 other patients Slight or

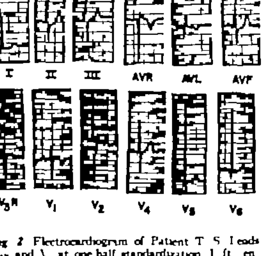


Fig 2 Electrocardiogram of Patient T S Leads V3R and V at one half standardization Left ventricular hypertrophy on the basis of increased voltage of S in Lead V1 and R in Lead V

minimal left atrial enlargement was present in 7 patients. Pulmonary vascularity was moderately increased in 4 patients, slightly increased in 4, and normal in 4. The pulmonary vascular markings were noted to become less prominent from age 10 to age 17 years in 1 patient (D P).

Hemodynamic findings (Table III). Catheterization of the right side of the heart was carried out in all patients, and the findings are given in Table III. Pulmonary arterial systolic pressures were moderately elevated in 2 patients (44 and 62 mm Hg). Of the 10 patients in whom technically adequate pull back pressure tracings from pulmonary artery to right ventricle were recorded, 6 demonstrated a systolic pressure gradient varying from 15 to 46 mm Hg. In 2 the gradient was at the pulmonary valve level, whereas in 4 it was observed

Table II. Electrocardiographic data

Patient	Age ECG (yr.)	Axis (degrees)	R/S in V_1	$S_{V_1}+R_{V_6}$ (mm.)	R_{V_6} (mm.)	Q_{V_6} (mm.)	T in V_1	T in V_6	S-T abnormal	LAE	VE
R A	5	+80	3	50	18	4	↑	↓	0	0	LVE
R S	8	+45	1	40	30	1		↓	+	0	LVE
S E	8	+85	1	50	30	?	Tall	↓	0	0	LVE
D W	6	+ 0	7	45	?0	4	[illegible]	↓	0	0	LVP
R G	11	+80	3	51	50	5	Tall	↓	+	0	LVE
A Z	7	+90	7	48	21	2	↑	↓	0	0	LVE
H K	11	+45	?	?6	54	4	↑	↓	0	0	LVE
T S	12	+45	5	50	35	10	Tall	[illegible]	+	0	LVE
D S	16	+60	3	35	20		↑	↑	0	0	None
D I	16	+65	3	55	35	5	↑	↑	+	0	LVE
F M	13	+60	5	50	30	6	↓	↑	+	0	LVE
I J	18	+80	2	39	3?		↑	↑	0	0	None

VE, Ventricular [illegible] enlargement; LAE, Left atrial [illegible]; LVE, Left ventricular [illegible]; LVP, Left [illegible] preponderance; [illegible] $S_{V_1}+R_{V_6}$ [illegible] 45 [illegible] mm [illegible] left ventricular [illegible]

Table III. Hemodynamic data

Patient	Age (yr.)	Femoral artery: O_2 saturation (per cent)	Femoral artery: Pressure (mm. Hg)	QP/QS	Pressure (mm. Hg): Low RV	Pressure (mm. Hg): High RV	Pressure (mm. Hg): PA	Retrograde angiographic findings
R A	5	96	1??/46	1 3	64/5	18/0	18/7	AI
R S	5	94	130/40	2 0	70/?	70/?	62/18	AI
S F	6	??	98/54	1 5	33/4	24/5	24/8	AI
D W	6	9?	1 3/53	1	30 8	30/8	33/11	AI small
R G	7	93	130/?8	1	44/0	44/0	44/17	Sinus [illegible] Valsalva to RV fistula ( )
A Z	7	91	13 /38	1 8	65/1	?0/1	?0/8	AI severe
H K	11	98	140/70	1 5	45/?	45/?	?4/5	AI [illegible]
T S	7	95	149/61	2 [illegible]	24/0	24/0	28/0	—
D S	17	96	150 60	1 ?	34/8	34/8	33 13	AI
D I	15	94	160/80	1 6	50/4	50/5	30/18	AI
F M	9	94	119/18	1 8	35/2	45/2	3? 19	AI severe
I J	16	9?	118/7	1 3	30/6	2/4	?0 9	—

[illegible] left [illegible] right [illegible] [illegible] by [illegible]
RV, Right [illegible]; PA, Pulmonary artery; AI, Aortic insufficiency

on pull back from the high to the low right ventricular position. The femoral arterial pulse pressure was 60 or greater in 10 patients and 52 and 44 mm. Hg in the other 2. The magnitude of the left to right shunt was found to be moderate in all with the pulmonary flow one and one half to two times systemic flow. In 1 patient (D. W.) the left to right shunt was inferred by intracardiac phonocardiography and by angiocardiography but not by blood oxygen analysis.

Aortography (*Fig. 4*). Retrograde aortography was carried out in 11 patients. Aortic regurgitation was roughly estimated to be marked in 4, moderate in 4, and slight in 1, on the bases of a qualitative estimation. Dye was observed to pass from the left ventricle into the right ventricular outflow tract and pulmonary artery in 7 patients, which indicated a left to right shunt at the ventricular level.

Anatomic findings. The anatomic findings in the 8 patients who underwent open heart surgery are as follows. The ventricular septal defect was high membraneous and approximately 1 cm. in size in 6 patients. In most instances the defect lay beneath the septal band of the crista supraventricularis, but in 3 patients it was superior to the crista. In 1 patient the defect was described as large but was closed by direct suture. A ventricular septal defect superior to the crista was repaired with a Teflon patch in 1 patient in whom the sinus of Valsalva had ruptured into the right ventricle and the right cusp of the aortic valve was prolapsed.

The aortic insufficiency was due to prolapse of the right cusp in 2 and of the noncoronary cusp in 4. In 1 patient the cusp involved was not indicated and in 1 it was stated to be the left cusp. The prolapsed cusp was repaired by direct suture except in 2 patients in whom it was not repaired. One patient (T. S.) died in the immediate postoperative period and no postmortem examination was performed.

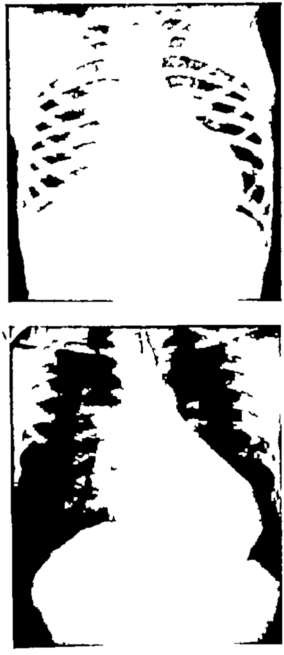


Fig. 3. Patient T. S. *Above*, Chest x-ray film at age 4 years showing left ventricular hypertrophy with moderately increased pulmonary vascularity. *Below*, Chest x-ray film at age 10 years showing progressive aortic dilatation.

Comment

Early reports of the combination of a ventricular septal defect with aortic insufficiency emphasized the difficulties inherent in the differential diagnosis between patients with continuous and those with to and fro murmurs.[3] More recently, with increasing study of the left heart and surgical repair of these lesions, the emphasis has shifted to hemodynamic aspects, natural history, and surgical considerations.

In our series the findings at catheterization and operation confirm the reports of others of patients in whom the ventricular left to right shunt is of small to moderate magnitude and the aortic incompetence is the hemodynamically significant component.[4,8] In addition the associated lesion of pulmonary stenosis which has been described[1] was observed in half of our patients usually it was due to mild infundibular stenosis but in 1 patient it was compatible with the presence of a muscular band.

In an attempt to clarify the natural history of this combination of defects we sought to ascertain the time of onset of the aortic diastolic murmur which is the time when the insufficiency becomes clinically recognizable. In 7 patients in our series this was documented to occur in early childhood from 2½ to 9 years of age coincident in the majority with the development of peripheral signs of insufficiency. Radiographic and electrocardiographic evidence of left ventricular hypertrophy had been present in the majority of patients prior to the onset of the diastolic murmur probably as a reflection of the left to right shunt and no changes were noted coincident with the recognition of regurgitation.

Symptomatology such as exercise intolerance did not correlate with other observations. Growth retardation commonly found in patients with left to right shunts was conspicuous and did not correlate with the severity of the aortic incompetence as estimated by pulse pressure and aortography.

The radiographic signs of a left to right shunt were minimal to moderate in all patients corresponding to the presence of a moderate left to right shunt.

An apical mid-diastolic flow murmur was heard in 7 of our patients and has been noted by others despite the relatively small shunt. Although this was not the presystolic murmur as originally described by Austin Flint it is possible that the increased flow across the mitral valve from the left to right shunt combined with the ballooning of the prolapsed aortic cusp against the mitral valve to produce the mid-diastolic murmur. A prediction of which cusp is insufficient on the basis of the transmission of the aortic diastolic murmur or the mid-diastolic murmur is considered to be hazardous.[7] In none of our patients was there clinical evidence of pulmonary stenosis although rarely



Fig. 4. Patient H. K. Retrograde aortogram. Anteroposterior (above) and lateral (below) [illegible] showing reflux of contrast material from aorta into the left ventricle.

this may be suspected on physical examination.

The 12 patients in this series were followed in the cardiac clinic from 1 to 13 years after the diastolic murmur was recognized. In 2 instances progressive left ventricular hypertrophy was noted by electrocardiogram and chest roentgenogram in early adolescence. The majority, however, did not show progression through late childhood. In autopsy-proved cases increased symptomatology and death have usually occurred in the second or third decades, with a history of bacterial endocarditis in many instances.[3]

The optimal time for surgical correction of this combination of defects is still in question. From this small series it would seem that signs of rapidly progressive disease after the insufficiency is recognized occur rarely during childhood. The presence of a left-to-right shunt probably serves to increase the incompetence of a prolapsed right or posterior cusp of the aortic valve, however, over a period of time. In addition, bacterial endocarditis, which occurs in approximately 20 per cent of the patients with aortic insufficiency, may cause further destruction of the aortic valve and a rapidly downhill course.[9] With improvement in the surgical management of aortic valve disease, more definite recommendations for management of these children will be evolved.

Summary

Clinical, electrocardiographic, radiographic, and hemodynamic findings in 12 children with the combination of a ventricular septal defect and aortic insufficiency are presented. The left-to-right shunt was determined to be small or moderate in all, and significant aortic insufficiency was documented by aortography in 11 patients. Clinical indication of aortic insufficiency as manifested by an aortic diastolic murmur first appeared at an average age of 6 years in 7 patients, with concomitant widening of the pulse pressure in 4. Progressive left ventricular hypertrophy was noted electrocardiographically, with progressive cardiac hypertrophy and aortic dilatation on x-ray examination, in 2 patients. Progression of the hemodynamic disability does not appear to be common in childhood, however.

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Experimental and laboratory reports

Virus-like particles in the heart of a patient with cardiomyopathy

An electron microscopic and histochemical study

*Richard G. Hibbs, Ph.D.**
Victor J. Ferrans, M.D., Ph.D.
William C. Black, M.D.
John J. Walsh, M.D.
George E. Burch, M.D.
New Orleans, La.

The detailed morphologic characteristics of the cardiomyopathies are poorly understood and need further and more detailed study.[1] In most instances routine histologic methods have provided important but still inadequate information and for this reason we are applying the techniques of electron microscopy and histochemistry to the study of the cardiomyopathies. Preliminary investigations have already disclosed interesting features of the myocardial damage present in patients with cardiomyopathy,[2] but the clinical significance of these observations has yet to be established.

The primary purpose of this paper is to report the electron microscopic observation of virus-like particles in the myocardium of a patient considered to have alcoholic cardiomyopathy who died shortly after developing an infection of the respiratory tract. To our knowledge this constitutes the first description of virus-like bodies in human myocardium in spontaneously occurring disease.

Case report

W. T., a 51-year-old Negro man, noted the onset of signs and symptoms of heart disease in 1955. He was hospitalized several times between 1956 and 1961 at the Charity Hospital and the Veterans Administration Hospital in New Orleans for the treatment of heart failure of undetermined etiology. The final clinical diagnosis was alcoholic cardiomyopathy. He was admitted to the United States Public Health Service Hospital in New Orleans in July, 1961, where he was placed on a therapeutic program of prolonged bed rest and the usually accepted treatment for congestive heart failure. After improvement on bed rest, he was discharged in June, 196[illegible]. No definite etiological basis for his heart disease could be established in spite of extensive effort.

The patient did well at home until August, 196[illegible], when he developed rhinorrhea, severe dyspnea, vague pain in the right side of the chest, and cough productive of mucoid sputum that was slightly blood tinged on one occasion. He was readmitted to the United States Public Health Service Hospital where examination disclosed moderately severe respiratory distress and distention of the neck veins. Decreased breath sounds and slight tenderness to percussion were noted at the right base, but no rales or friction rubs were heard. Marked cardiomegaly, left ventricular heave, Grade 1 blowing apical systolic murmur, and an early diastolic

From the Department of Anatomy and Medicine, Tulane University School of Medicine, [illegible] Charity Hospital of Louisiana, and the [illegible] Memorial Research Laboratories of the United States Public Health Service Hospital, New Orleans, La.

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*Address: Department of Anatomy, Tulane University School of Medicine, 1430 T[illegible], New Orleans, La. [illegible]

gallop rhythm were found on examination of the heart. The liver was enlarged to 8 cm below the right costal margin. The remainder of the examination was unremarkable.

Hospital course. The patient responded well initially to therapy with penicillin, expectorant, digitalis, and mercurial diuretic, with disappearance of the cough and the chest pain. He remained essentially asymptomatic until 4 days prior to his death, when he began to experience mild respiratory distress, although physical examination of the chest failed to reveal any new changes. The dyspnea increased and a dry cough developed, followed by marked venous distention, tachypnea, gallop rhythm, and tachycardia. He failed to respond to therapy, became comatose, and died suddenly on the evening of Oct. 4, 1962.

Autopsy. Pertinent findings at postmortem examination performed 1 hour after death were limited to the heart, lungs, and liver. The heart weighed 560 grams. The coronary vessels were pliable and free of obstruction. All cardiac chambers were markedly dilated. The valvular ring measurements were tricuspid 13.5 cm, mitral 13.0 cm, pulmonary 9.0 cm, and aortic 9.0 cm. The valves, chordae tendineae, and the papillary muscles were normal. Examination of the left ventricular endocardial surface revealed a grayish thickening that was most marked in the septal wall but also extended to the apex and the lateral wall. A thrombus was noted in the right atrial appendage. The left ventricle measured 16 mm in thickness, the right ventricle 5 mm. The myocardium was flabby and had a diffuse yellowish appearance. The right lung weighed 550 grams, the left 519 grams. There was an embolus in the branch of the pulmonary artery supplying the right lower lobe. Bilateral pulmonary edema and bronchopneumonia were present. The liver weighed 1,270 grams. Its surface was smooth, its consistency firm, and marked congestion was evident on cut section.

Histologic examination of the myocardium revealed many areas of marked edema of the muscle fibers (Fig. 1). Separation of the myofibrils (Fig. 1 *B, C, D*), numerous vacuoles (Fig. 1 *B* and *C*), and a granular appearance with loss of the cross striations were evident in the cytoplasm of the muscle cells. The morphology of the nuclei (Fig. 1 *A, B, C*) was extremely variable: many were small, others were large and vesicular with a wrinkled outline, and still others had bizarre rectangular or square shapes. No inclusion bodies were observed. A few areas of fibrosis were noted with isolated muscle fibers scattered throughout the connective tissue, which appeared to be edematous and loose in texture. Very few inflammatory cells were present in the myocardium; the subendocardial connective tissue contained a few round cells in some areas. Sections of the right atrial appendage showed a thrombus attached to its endocardial surface.

Histochemical and electron microscopic studies

Materials and methods. Tissues collected for histochemistry were frozen rapidly and sectioned at a thickness of 6 to 10 μ in a cryostat. The following techniques were employed: (1) Phase contrast and polarization microscopy for observation of tissue structure. (2) Fluorescence microscopy for study of the autofluorescence of lipofuscin[6] and elastic tissue fibers. (3) PAS reaction for polysaccharides. (4) Toluidine blue staining for metachromasia. (5) Plasmal reaction for plasmalogens.[7] (6) Benzpyrene caffeine,[8] phosphine,[9] and Nile blue sulfate[10] staining for the fluorescence microscopy of lipids. (7) Staining reactions for succinic dehydrogenase,[11] cytochrome oxidase,[12] diphosphopyridine nucleotide diaphorase,[13] and for several pyridine nucleotide linked dehydrogenases (isocitrate, malate, lactate, glutamate, and ethanol dehydrogenase).[13]

For electron microscopy the tissues were cut in 0.5 mm. cubes, fixed in phosphate buffered osmium tetroxide,[14] dehydrated through a graded series of alcohols and embedded in Maraglas.[15] Sections were cut with an LKB ultratome and examined with an RCA EMU 3C electron microscope.

Histochemical observations. The amount of lipofuscin present in the heart muscle cells was normal for the patient's age. PAS and toluidine blue stains also appeared to be normal. Fluorescence microscopy revealed (Fig. 2) marked diffuse intracellular accumulation of lipid droplets in the atrial and ventricular myocardium. The lipid deposition was slightly more pronounced in the subendocardial areas than elsewhere. The smaller lipid droplets were arranged in parallel rows in the interfibrillary spaces, whereas the larger ones seen in more severely diseased cells occupied much greater portions of the cytoplasm. The size of the large lipid droplets (Fig. 2 *D*) corresponded to that of the vacuoles noted (Fig. 1 *B*) in the hematoxylin eosin preparations. The zones of fibrosis were free of lipid deposits, as were the few round cells present in those areas. By comparison to normal human heart muscle the plasmal reaction was considerably less intense throughout most of the myocardium. The lipid droplets and the lipofuscin granules were plasmal negative.

Histochemical staining for succinic dehydrogenase, cytochrome oxidase, DPN diaphorase, and the pyridine nucleotide linked dehydrogenases demonstrated a



Fig. 1. Four views of left ventricular myocardium hematoxylin-eosin ×800. A Area showing normal fibers (F) in contrast to a fiber (D) with early degenerative changes. Note the [illegible] nuclear morphology. B Pronounced vacuolization (V) and varying degrees of edema are seen in several cells. The vesicular appearance of nuclei (N) is evident. C Zone of more [illegible] damage showing marked edema of fibers (E), numerous vacuoles (V) and the irregular shape of a nucleus (N). D Longitudinal section of two myocardial cells. The myofibrils of the (M) still retain their cross-striations whereas those in the edematous fiber (E) are very indistinct and irregular. Numerous vacuoles (V) are seen between the myofibrils.

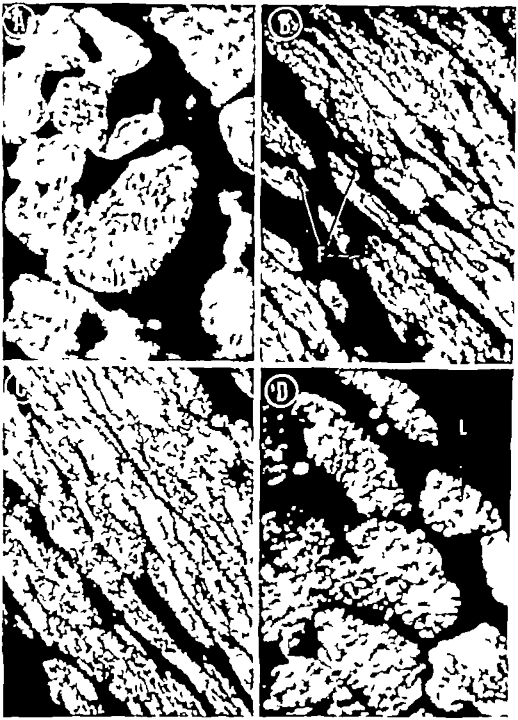


Fig 2 Fluorescence photomicrographs of myocardium stained with benzpyrene for the fluorescence microscopy of lipid A Normal human myocardium shown here for purposes of comparison Cross-section of normal muscle fibers demonstrating the pattern of interfibrillary staining and the absence of lipid droplets ×1 200 B Low power view of left ventricular myocardium showing a moderately severe degree of lipid deposition involving most of the muscle cells Only a few relatively normal fibers (*F*) can be seen ×100 C Area similar to *B* but more heavily and diffusely laden with lipid deposits ×200 D High power view of degenerating muscle cells containing large numbers of lipid droplets of various sizes ×800 Compare with Figs 1 *B* and *C* and 2 *A*

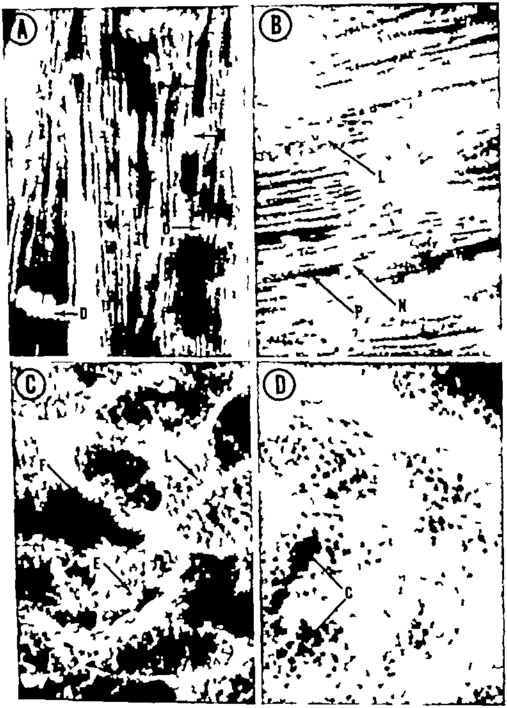


Fig 3 Succinic dehydrogenase preparations from left ventricular myocardium ×800 *A* Longitudinal section of normal human myocardium showing the localization of the reaction to the muscle mitochondria Note the intense mitochondrial reaction in the perinuclear zone (*P*) at the poles of the unstained nucleus (*N*) The intercalated discs (*D*) are also unstained *B* Area similar to that of Fig 1 *D* Longitudinal section of myocardial fibers demonstrating the marked disruption of the staining pattern (compare to Fig 3 *A*) and the irregular decrease in the intensity of the reaction Formazan deposits can be seen adjacent to the lipid droplets (*L*) and at the poles (*P*) of the nucleus (*N*) The intensity of the perinuclear reaction is decreased *C* Cross section of myocardial cells showing normal fibers (*F*) lipid droplets (*L*) and varying degrees of loss of enzyme activity in edematous fibers (*F*) Compare with *A* and *B* of Fig 1 *D* Cross section of damaged muscle fibers showing very little enzyme activity in clumps (*C*) of formazan deposits Compare with Fig 1 *C* and 2 *D*

marked depression of the intensity of the reactions for all these enzymes. These changes were best seen in the succinic dehydrogenase (Fig. 3) and isocitric dehydrogenase preparations. The changes in oxidative enzyme activity were observed throughout the myocardium but varied in degree from one area to another (Fig. 3 C).



Fig. 4. A low power electron micrograph from an area of myocardial degeneration. Note the numerous large lipid droplets (L) between the myofibril. The contractile elements appear to be essentially normal. ×10,000.

and were particularly prominent in the zones most heavily affected by the lipid deposition. Interpretation of the results obtained with the dehydrogenases especially with succinic dehydrogenase was complicated by the deposition of formazan granules at the periphery of the lipid droplets (Fig. 3 B) even though tetranitro

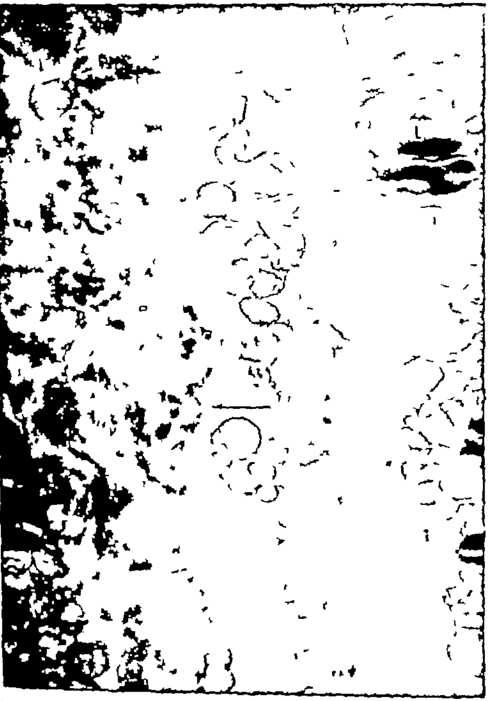


Fig. 3 Part of a damaged myocardial cell showing lipid droplets (L) and an area of disruption of the myofilaments (arrow) ×18 000

BT was also used to minimize this problem.[11] Clear outlines of weakly reacting swollen and partially disrupted mitochondria were observed in sections extracted with cold acetone prior to the enzymatic incubation.

Electron microscopic observations. Electron microscopic studies revealed considerable morphologic variations from one area of the myocardium to another. Muscle fibers from areas containing the least lipid were essentially normal in appearance. A few lipid droplets of less than 0.5 μ in diameter were present in the interfibrillary spaces in close apposition to the mitochondria. Large lipofuscin granules measuring up to 4 μ in diameter were encountered occasionally. The contractile elements appeared to be unaltered. The only noticeable change in many of these cells was slight swelling and loss of the cristae in some of the mitochondria.

Cells in areas heavily laden with lipid showed the most pronounced alterations. Numerous lipid droplets up to as much as 4 μ in diameter were present throughout the cytoplasm of the muscle fibers (Fig. 4). The droplets were not membrane limited and were located in the interfibrillary spaces, often encroaching on the space normally occupied by the myofibrils, which followed irregular courses between the lipid droplets. The myofibrils showed patchy areas of disruption of myofilaments which varied in length from that of one sarcomere to several microns (Fig. 5). These areas of dissolution usually extended across several myofibrils and sometimes across the entire width of the cell.

The mitochondria varied a great deal in size, shape, and distribution. A few were normal in appearance, but most of them showed moderate to severe swelling and loss of the cristae. The number of mitochondria present per unit area was somewhat greater than in normal myocardium. The endoplasmic reticulum was essentially normal in appearance except in areas of disruption of myofilaments, in which the reticulum consisted of small vesicles of irregular shape and distribution.

Numerous membrane-enclosed particles measuring approximately 30 mμ in diameter were present throughout the muscle fibers in the most severely damaged areas (Fig. 6). These particles were most numerous just under the sarcolemma, but were also observed in large numbers in the interfibrillary spaces. They were found most often singly, each one enclosed by a membranous capsule, and closely resembling the classic "target" form of virus particles. In addition to the single forms, multiple particles, usually two or three of the same type, were often encountered enclosed in a single membrane. Still another form in which these same particles were occasionally encountered was in large clusters of fifty or more particles enclosed by multiple concentric membranes resembling myelin figures (Fig. 6 C). Most of the particles found near the sarcolemma were singles or doubles (Fig. 6 A and B), whereas the multiple forms were usually located more deeply within the muscle cells.

Discussion

The histochemical and electron microscopic alterations described above represent profound, diffuse myocardial damage. The functional aspects of this injury were best demonstrated by the histochemical studies of the intramitochondrial enzymes. The loss of these enzymes indicated gross derangement of mitochondrial function, and indeed electron microscopy showed corresponding evidence of widespread abnormalities of mitochondrial structure. The combination of myocardial fatty change and the pattern of injury described above has been reported in a series of patients with alcoholic cardiomyopathy in a preliminary communication from these laboratories.[8] These observations, to be presented in detail elsewhere, are in agreement with the biochemical studies of Wendt and co-workers.[17]

The clinical course of this patient, which prior to his last admission had been similar to that of other patients, was sharply altered by the infection of the respiratory tract that preceded and possibly precipitated his death. It is regrettable that viral studies were not obtained during the patient's illness. Attempts at isolating a viral agent from the myocardium after death were unsuccessful and probably inadequate because of lack of anticipation of the electron microscopic findings. In the absence of microbiologic proof it is

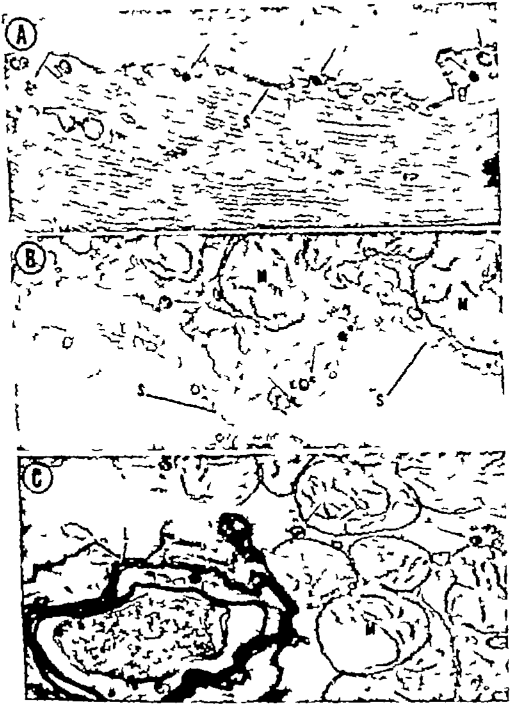


Fig 6 A Higher magnification of the edge of a myocardial cell showing several encapsulated virus like particles (arrows) just under the sarcolemma (S) ×35 000 B Part of two adjacent myocardial cells Note the encapsulated particles (arrows) under the sarcolemma (S) and the greatly swollen mitochondria (M) ×30 000 C An area from the interior of a myocardial cell showing swollen mitochondria (M) and numerous particles enclosed within multiple lamellae (L) Other encapsulated particles (arrows) are also present ×28 000

impossible to state with certainty that the particles observed in the myocardium were actually viruses However several reasons have led us to the conclusion that these particles were viruses (1) These particles which were distinctly different from lipofuscin glycogen and ribosomes did not have the characteristics of any substance known to occur in myocardium in granular form (2) No membrane enclosed particles such as these have ever been described in myocardium and none have been previously encountered during the examination of a large number of normal and pathologic human and animal hearts in these laboratories (3) Their morphology especially that of the single forms was typical of many viruses[1] (4) Their size (30 mμ) compared well with that of many of the smaller viruses such as those of the polio and Coxsackie groups both of which have a diameter of about 27 mμ [3]

It is impossible to establish the nature of the relationship that existed between these virus like particles in the myocardium and the patient's illness They might have presented either dormant or active viruses totally unrelated to the clinical situation or active forms responsible for at least part of the heart disease They could have played a causal or contributory role in the etiology of the cardiomyopathy the terminal episode or both These questions remain unsolved If these particles were truly viruses their preferential distribution in severely damaged muscle cells lends support to the idea that they probably had only recently invaded the myocardium

Infections of the respiratory tract are frequently important precipitating factors in the death of patients with all types of cardiac disease It is possible that death may be caused in some patients by a viral myocarditis superimposed upon an already damaged heart

Summary

Virus like particles measuring 30 mμ in diameter were observed by electron microscopy in the heart muscle cells of a patient who probably had alcoholic cardiomyopathy and who died shortly after developing an infection of the respiratory tract Additional histochemical and electron microscopic studies of the myocardium revealed marked cellular damage manifested as varying degrees of lipid deposition mitochondrial swelling and fragmentation loss of intramitochondrial enzymes and disruption of the contractile elements The significance of these observations was discussed

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Studies on the physiopathology of experimental pulmonary embolism

1. Pulmonary and systemic hemodynamics

E. Vitolo, M.D.*
E. Gola, M.D.
F. Valentini, M.D.
Milan, Italy

It is already generally agreed that the consequences of the occlusion of a large branch of the pulmonary artery (or of its main trunk directly) have a mechanical pathogenesis that is due directly to the sudden and complete reduction in the vascular pulmonary bed. On the contrary, the problem set by the nature of phenomena which result from the embolism of small branches of the pulmonary artery is yet far from being solved. As far as the hemodynamic alterations of the pulmonary circulation are concerned, there is a whole series of arguments supporting the reflex origin—neurogenic or humoral—of such hemodynamic alterations[1-10]; however, there are investigators who disagree and who support the mechanical origin which is closely linked to the exclusion of a region of the vascular pulmonary bed due to the embolus or to single embolic particles.[11-15]

Even with regard to alterations in the systemic and coronary circulations, opinions are still divergent, and for these two aspects of the problem also there are two main theories, one of which explains the alterations as secondary to a reflex of pulmonary origin and the other on a mechanical basis only. The obvious practical value of such problems is their consequence in the therapeutic field. But they have great theoretical interest as well because of the number and importance of the problems which thereby become involved: pulmonary innervation, existence of reflex mechanisms that regulate the various regions of the blood circulation, action of the sympathetic and parasympathetic systems on those regions, release of humoral substances and their activity, and so on.

On the basis of these preliminary considerations we thought that it would be useful to attempt, through a series of experimental investigations, to solve the problem concerning the nature of the alterations observed in the pulmonary and systemic hemodynamics, in the coronary circulation, and in the pulmonary ventilation as the consequence of pulmonary embolization. In the present study, performed on closed-chest anesthetized dogs, we examined the pressures in the catheterized pulmonary artery and veins and in the femoral artery after occlusion of one lobar branch of the pulmonary artery with a balloon and successively after having injected an embolus beyond

From the Institute of Medical Pathology, University of Milan, Milan, Italy.
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*Address: Università di Milano, Istituto di Patologia Medica, Via Francesco Sforza 35, Milano, Italy.

this inflated balloon thus into a vascular territory already excluded from the pulmonary circulation

Methods

The experiments were carried out on 25 medium sized and large adult dogs under chloralose anesthesia. Two catheters were introduced through a jugular external vein. The first one was a Dotter Lukas double lumen catheter. It had an inflatable rubber balloon close to the tip and the other lumen opening 4 cm proximal to the balloon was for the recording of pressure. This catheter was inserted in such a way as to have its opening correspond to the trunk of the pulmonary artery so that the balloon was thus within one of the lobar branches of the artery and precisely in the inferior left lobar branch. The second catheter had a single lumen and was inserted into the same vessel closely distal to the balloon of the first catheter. A third catheter was introduced into a common carotid artery and in retrograde fashion was thrust into a pulmonary vein for the recording of pressure. The mean pressures in the pulmonary artery and veins were determined with Sanborn electromanometers and were continuously and simultaneously recorded on a Sanborn Twin Viso apparatus. In this way we were able to observe the behavior of the pulmonary arteriovenous gradient during the whole experiment.

To measure the systemic blood pressure (systolic values) a glass cannula was tied into a femoral artery and connected with a mercury manometer.

After basic values of pressure had been recorded and while the recording was proceeding continuously the balloon was filled with 0.5 to 1 c.c. of Pielosil (diodone 50 per cent) in order to occlude entirely the corresponding vessel. This occlusion lasted until the end of the experiment. After the pressure values were stabilized in view of previous changes but never before 15 minutes had elapsed after inflation of the balloon embolization was performed. This was accomplished by injecting through the single lumen catheter and then distally to the balloon in the previously occluded artery 5 to 10 c.c. of barium sulfate and iron perchloride suspension in normal saline solution[1,7,4]. Pressures were recorded for a period of time varying between 30 and 60 minutes or until the animal's death if that occurred sooner.

The hemodynamic results obtained (mean pressure in the pulmonary artery and veins, arteriovenous pulmonary gradient and systolic pressure in the femoral artery in millimeters of mercury, and for each of these the values before and after occlusion with the balloon and before and after embolization) and also the time data of the various phenomena were analyzed statistically. We evaluated the arithmetic mean ($\bar{x}$) and the standard deviation (s) and the significance of the modifications obtained was determined by Student's t test. As usual we designated as non significant the variations whose probability of being due to chance was greater than 5 per cent ($p > 0.05$), as significant the variation with probability greater than 1 per cent ($p > 0.01$) and as highly significant the variations with probability less than 1 per cent ($p < 0.01$).

At the end of the experiment a histologic examination of the lungs was performed. In some dogs specimens were obtained from the embolized lobe, from the other lobe of the same lung and from the contralateral lung. After fixation in formalin and embedment in paraffin the slides were colored with hematoxylin-eosin.

Results

The results of the individual experiments are summarized in Table I. Tables II and III show the results of the statistical analysis of the hemodynamic data and the time correlations. Fig. 1 is an example of the pressure record.

Pulmonary artery. After occlusion with the balloon the pressure in the pulmonary artery increased in 18 of 25 cases with a mean increase of 3.6 ± 3.4 mm Hg which is highly significant statistically; it began quite early (2.6 ± 4.7 seconds) and reached a peak after 21.7 ± 9.4 seconds.

After the subsequent embolization a further increase in pressure occurred in all 25 cases with a mean increase which was highly significant also but which was much higher than the first, 29.4 ± 14.1 mm Hg. At the same time this increase

Table 1 Pressure values (in mm Hg) and time values (in seconds) in the individual experiments

Number of cases	Method	Pulmonary artery			Pulmonary vein			Artery-venous pulmonary gradient			Femoral artery			Time of onset			Time of maximum effect		
		Before	After	Diff	Before	After	Diff	Before	After	Diff	Before	After	Diff	Pul artery	Pul veins	Fem artery	Pul artery	Pul veins	Fem artery
24	Balloon	18	18	0	5	[illegible]	[illegible]	13	11	–	270	80	0	–	1	20	—	5	40
	Embolism	18	6	+1	2	8	−2	16	6	+19	200	10	−160	1	11	20	20	20	60
25	Balloon	20	20	+10	10	10	0	10	20	+10	180	190	0	1	—	—	100	–	—
	Embolism	28	[illegible]	+2	[illegible]	8	[illegible]	23	[illegible]	+12	180	170	4	1	1	—	20	8	—
28	Balloon	12	12	0	5	0	−5	7	12	+5	190	190	0	–	?	—	—	?	–
	Embolism	10	0	+10	8	−2	−2	10	12	+12	170	100	20	1	8		15	30	
29	Balloon	[illegible]	20	+8	0	2	+2	12	18	+6	[illegible]	[illegible]	0	1	?	—	3	?	—
	Embolism	20	3	+13	8	−2	−2	[illegible]	[illegible]	+1	120	20	−100	1	1	1	1	8	35
30	Balloon	12	12	0	0	0	0	12	12	0	100	100	0		—	—	—	—	—
	Embolism	13	3	+23	2	0	−2	10	3	[illegible]	100	20	80	1	1	8	1	20	10
31	Balloon	18	22	+4	1	3	[illegible]	[illegible]	19	[illegible]	130	130	0	1	?	—	15	?	—
	Embolism	20	10	+20	8	8	+8	20	12	+12	[illegible]	[illegible]	0	1	1	—	200	3	—
32	Balloon	10	13	+3	2	−5	−7	8	18	+10	115	115	0	1	20	—	20	90	—
	Embolism	12	12	+20	8	−2	+6	20	31	+11	110	60	50	2	20	1	1	10	50
33	Balloon	15	25	+7	10	5	−5	9	20	+12	115	100	15	1	1		3	25	100
	Embolism	20	8	+6		−2	–	13	[illegible]	[illegible]	100	10	90	1	1	1	150	1	20
36	Balloon	17	0	+3	0	0	0	12	20	+8	180	180	0	1	—	—	8	—	—
	Embolism	16	10	+11	0	0	0	16	30	+11	180	150	−30	10	—	20	35	—	150
37	Balloon	17	28	+11	5	1	−2	12	25	+13	150	150	0	5	13	—	10	50	—
	Embolism	30	1	+1		8	+3	25	3	+12	[illegible]	20	[illegible]	1	16	10	2	30	160
38	Balloon	12	12	0										—			—		
	Embolism	13	30	+1	0		−7	13	17	+21				1	21		1	13	

39 [illegible]	4 8	7 31	+3 +26	−2 [illegible]	2 −1	0 −1	[illegible] [illegible]	9 [illegible]	+3 +[illegible]	160 160	70 50	0 −110	70 10	— 30	— 10	80 200	200	600
40 [illegible]	18 1	0	+2 +60	2 2	2 2	0 0	16 13	18 3	+2 +60	150 1 0	150 30	0 −130	1 1	— —	— 68	1 10	— —	— 160
41 Balloon	10	18 [illegible]	+8 +2	1 3	4 7	+1 +1	7 1	14 23	+7 +21	110 100	1 0 30	0 −70	1 1	8 —	— 3	10 136	41 —	— 36
42 Balloon	4	7 1	+2 +30	0 0	0 [illegible]	0 +2	5	7 33	+2 +28	170 120	120 10	0 −80	1	— 60	— 19	3 80	— 12	— 10
43 [illegible]	18 1	18 2	0 +37	7 [illegible]	7 10	0 +7	11 8	11 13	0 +31	160 160	160 90	0 −70	— 6	— 10	— 10	— 320	— [illegible]	— 800
44 [illegible]	12 1	15 18	+3 +36	0 −2	0 —	0 −3	12 11	15 1	+3 +39	125 120	125 20	0 −100	1 8	— 16	— 9	6	— 68	— 6
45 [illegible]	18 1	20 10	+2 +2							140 110	140 120	0 −20	8 12		— 11	90 300		— 300
46 [illegible]	5 8	5 38	0 +30							110 130	80	−25 [illegible]	— 12		100 112	— 10		200 500
47 [illegible]	30 30	35 10	+5 +30							125 120	125 90	0 −30	1 10		— 100	2 1		— 1 300
48 [illegible]	7	9 23	+2 +15							130 130	130 100	0 −30	1 1		— 3	2 36		— 72
49 [illegible]	15 2	19	+4 +18							130 110	130 20	0 120	1 1		— 10	1 16		— 20
50 Embolism	15 28	22 3	+7 +1							170 100	120 20	0 80	1 1		1	2 1		— 28
51 [illegible]	5 7	10 0	+2 +15							100 9	90 8	10 −1	1 8		90 100	2 160		90 180
52 [illegible]	11 10	11 25	0 +18							105 10	105 20	0 8	— 1		— 5	— 10		— 600

[illegible]

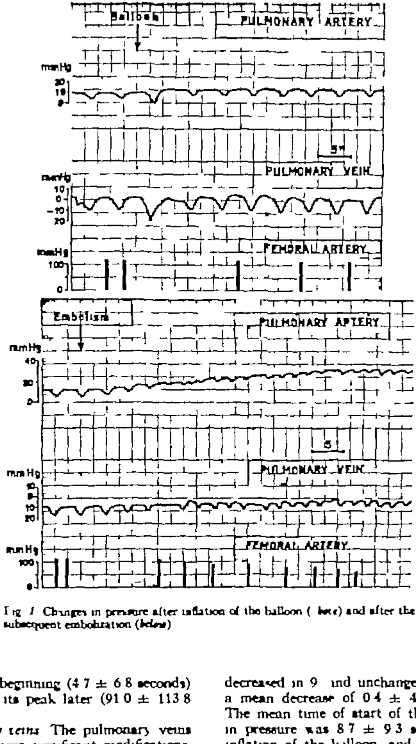


Fig. 1. Changes in pressure after inflation of the balloon (above) and after the subsequent embolization (below).

had a rapid beginning (4.7 ± 6.8 seconds) but reached its peak later (91.0 ± 113.8 seconds).

Pulmonary veins. The pulmonary veins did not undergo significant modifications neither after inflation of the balloon nor after the embolization. After occlusion with the balloon the pressure was increased in 4 cases, decreased in 4 others, and unchanged in 8, with a mean decrease of 0.7 ± 2.6 mm. Hg, whereas after the embolization it was increased in 6 cases, decreased in 9, and unchanged in 2, with a mean decrease of 0.4 ± 4.3 mm. Hg. The mean time of start of these changes in pressure was 8.7 ± 9.3 seconds after inflation of the balloon and 24.0 ± 27.4 seconds after the embolization, whereas their peaks were respectively at 13.2 ± 36.6 and of 43.8 ± 176.2 seconds.

Pulmonary arteriovenous gradient. As a consequence of this modification in pressure, the pulmonary arteriovenous gradient had a highly significant increase

either after inflation of the balloon or after embolization but after the embolization the increase was much higher than that recorded after inflation of the balloon with a mean increase respectively of 30.8 ± 17.1 and 5.0 ± 4.5 mm Hg In particular after inflation of the balloon the pulmonary arteriovenous gradient was

Table II Values of changes in pressure (in mm Hg) due to inflation of the balloon and to embolization

	Balloon			Embolism		
	Before	*After*	*Difference*	*Before*	*After*	*Difference*
Pulmonary artery						
x̄	13.4	17.1	+3.6	14.9	44.2	+29.4
	5.5	7.9	3.4	[illegible].0	15.3	14.1
P			<0.01			<0.01
n	25	25	25	25	25	25
Pulmonary veins						
x̄	3.0	2.2	−0.7	1.2	0.7	−0.4
	3.6	3.7	2.6	3.4	4.8	4.3
P			>0.05			>0.05
n	16	16	16	17	17	17
Arteriovenous pulmonary gradient						
x̄	10.5	15.5	+5.0	14.1	45.0	+30.8
s	3.4	4.9	4.5	6.1	16.9	17.1
P			<0.01			<0.01
n	16	16	16	17	17	17
Femoral artery						
x̄	136.8	133.9	−2.9	131.6	61.6	−69.5
s	6.2	30.0	7.0	8.9	47.4	44.0
P			>0.05			<0.01
n	24	24	24	24	24	24

[illegible] (number of [illegible]) P = Probability (> 0.05 = [illegible] < 0.05 = significant < 0.01 = highly significant)

Table III Time of onset and time of maximum effect (in seconds) of the changes in pressure in the pulmonary artery pulmonary veins and femoral artery after inflation of the balloon and after embolization

	Balloon			Embolism		
	Pulmonary artery	*Pulmonary veins*	*Femoral artery*	*Pulmonary artery*	*Pulmonary veins*	*Femoral artery*
Onset						
x̄	2.6	8.6	51.7	4.7	24.0	58.9
s	4.7	9.3	45.2	6.8	27.4	101.5
n	18	5	4	5	14	21
Maximum effect						
x̄	21.7	43.2	122.3	91.0	43.8	146.3
s	9.4	35.6	95.4	113.8	176	363.7
n	18	5	4	25	14	21

Symbols as in Table II

increased in 13 cases, decreased in 1, and unchanged in 2, whereas after the embolization it was increased in all cases.

Femoral artery. After occlusion with the balloon the pressure in the femoral artery remained unchanged in 20 of 24 cases; in the other 4 it was slightly decreased. The mean decrease (2.9 ± 7.0 mm. Hg) is not statistically significant. The mean start of hypotension in the cases in which it developed was 51.7 ± 45.2 seconds after inflation of the balloon, whereas the peak was reached after 122.5 ± 95.4 seconds.

After embolization the pressure in the femoral artery dropped sharply in 22 cases, whereas in 2 cases only did it remain unchanged; the mean fall was 69.5 ± 44.0 mm. Hg, which is highly significant. After the embolization, 10 animals died. The beginning of the fall in pressure took place on an average after 58.9 ± 101.5 seconds, with the peak being reached after 346.3 ± 363.7 seconds.

After either inflation of the balloon or embolization the femoral arterial hypotension occurred at the same time (2 cases) or after the beginning of the pulmonary arterial hypertension (19 cases). The difference between the beginning of the hemodynamic changes in the pulmonary and in the systemic circulations (56.9 and 4.7 seconds, respectively, as already noted) is statistically significant. Because there were so few animals in which the drop in femoral arterial pressure occurred after inflation of the balloon (4 cases), we did not consider as being useful a statistical study on the time correlations between such a drop in pressure and the rise in pulmonary arterial pressure after that experimental maneuver.

Discussion

After occlusion of the inferior lobar branch of the left pulmonary artery with the balloon, the mean pressure in the pulmonary artery trunk showed a rise of 3.6 mm. Hg, which is highly significant statistically. Our results agree with those of Moreau[illegible] obtained under similar experimental conditions. On the contrary, our findings do not agree with those of Haynes and colleagues,[illegible] who, although occluding a lobar artery with a balloon, did not record any increase in pressure. Further-more, the increase in pressure which we obtained, although moderate (corresponding to 25 per cent of the basic pressure), necessitates an explanation if compared with some now well-recognized data of pulmonary hemodynamics. It was in fact observed that to obtain an increase in pressure in the pulmonary artery its circumference[illegible] must be reduced by 50 to 60 per cent or else the extent of the pulmonary vascular bed[illegible] must be reduced by 52 to 60 per cent. According to this we also know that excluding a whole lung from the circulation does not provoke any modification of pressure or, if any, only very slight and insignificant.[illegible] Some investigators disagree with these results because they have obtained with the same procedure a more or less severe pulmonary hypertension.[illegible]

It is very difficult, obviously, to explain our results merely on a mechanical basis; in fact, we obtained a pulmonary hypertension with the exclusion of a portion of the pulmonary vascular bed corresponding to 22.32 per cent of the whole,[illegible] which means half of what we found was necessary to obtain solely by a mechanical action a similar pressure response.

We think that it is logical, therefore, that a reflex factor was operative, produced by the hypotension developing distal to the occlusion, as Brofman and associates[illegible] have thought, or by the distention of the vessel caused by the inflated balloon. It is true that Hall and Ettinger,[illegible] Hara and Smith,[illegible] and Rovati and associates[illegible]—the latter considering solely the pulmonary artery bifurcation—observed that mechanical or electrical stimulation of the intima of the pulmonary artery did not provoke pulmonary hypertension, but other investigators have had contradictory results.[illegible]

It is not yet known in which section of the pulmonary arterial tree are to be found the nervous receptors which are able to provoke a spasm in the pulmonary artery. Although according to Weidner and Light[illegible] they are localized in vessels which vary in size between 100 and 25 microns, and for Whitteridge[illegible] they are near or in the arteriolar areas, Secbat and associates[illegible] believe that they lie in the lobar arteries, being absent only in the portion included

between the origin and the bifurcation of the main trunk of the pulmonary artery. But recent studies[71,78] demonstrate that nervous receptors are also localized in the main branches of the pulmonary artery. However it is possible that these receptors increased or became more sensitive as they progressed from the main branch to the finest ramifications of the pulmonary arterial tree.[1,18,17,31,75,81]

A higher reflexogenic capacity of the vessels of smaller size could explain the hypertensive response which we obtained by occluding a lobar artery, in comparison with the lack of a response noted by the afore-mentioned authors who occluded the main artery of a lung. The results of Moreau and associates,[68] Scebat and associates,[69] Osorio and Russek[71] and Moreau[68] might be interpreted likewise: they observed that the inflated balloon pushed far forward into the pulmonary arterial tree provoked a hypertensive response higher than that seen with the occlusion of a larger vessel and thus of a greater mechanical importance. This was observed by us also, although not systematically but only occasionally during three experiments. In Dog No. 36, inflation of the balloon in the lobar artery caused an increase of 8 mm. Hg in the pulmonary arterial pressure, whereas inflation in a distal branch provoked an increase of 15 mm. Hg, which was superior also to the increase of 14 mm. Hg provoked by the embolization. Since in this dog the pulmonary venous pressure never changed, the increases in the arteriovenous gradient were of the same degree as those in the artery. In Dog No. 37 also, inflation of the balloon in the lobar artery showed an increase of 11 mm. Hg in the pulmonary arterial pressure, whereas inflation in a distal branch showed an increase of 18 mm. Hg, which was also higher than the increase of 15 mm. Hg obtained later by embolization; the increases in the arteriovenous gradient were respectively proportional—13, 18 and 12 mm. Hg. Finally, in Dog No. 35, occlusion with the balloon of a distal branch of the pulmonary artery caused the animal's death after the following changes in pressure had been determined: a rise in pulmonary arterial pressure of 20 to 45 mm. Hg, a drop in pulmonary venous pressure of 0 to −5 mm. Hg and a rise in the arteriovenous gradient of 20 to 50 mm. Hg (femoral arterial pressure remained at the basic value of 150 mm. Hg). As can be seen, the values attained by the pulmonary arterial pressure and by the arteriovenous gradient after occlusion of a distal branch of the pulmonary artery are far greater than the highest values ever recorded after occlusion of a lobar artery.

Direct demonstrations were also given of the reflex mechanism that sustained the hypertension which followed the occlusion of a distal branch of the pulmonary artery. Thus Scebat and associates[69] showed angiocardiographically a diffuse vasoconstriction—therefore in the contralateral lung too—chiefly of the small-sized arteries and they suppressed the hypertension with protoveratrine. Similar suppression of the hypertensive response was obtained by Osorio and Russek[71] after denervation of the hilum of the pertinent lung.

Another mechanism, namely the differing distention of the balloon and thus of the occluded vessel, could explain the discrepancy of some results, for instance the lack of or moderate hypertension obtained by the afore-mentioned workers with the occlusion of a main branch of the pulmonary artery, in contrast to the severe hypertension obtained in the same way by others.[72,73,74] Likewise, it can be thought that the absence of the hypertension observed by Haynes and associates[15] in their first mentioned studies depended upon a lesser distention by the balloon in the lobar artery than that obtaining in our own experiment. Therefore we can conclude that the pulmonary hypertension which follows the balloon occlusion of a lobar branch of the pulmonary artery is due, at least in part and in the cases in which the dilatation exercised by the balloon in the vessel is greater, to a vasoconstrictor reflex brought about by the mechanical stimulation of the vessel walls by the balloon.

The increase in the arteriovenous pulmonary gradient shown in our experiments agrees with the interpretation of a vasoconstrictive basis for the pulmonary hypertension. But as for the value of the



Fig. 2. Artery from the nonembolized upper lobe of the embolized lung (×170).

arteriovenous gradient in indicating vascular pulmonary resistance we shall discuss that later when we deal with the results of the embolizations.

Occlusion with the balloon of a lobar branch of the pulmonary artery failed to provoke any changes in systemic arterial pressure. In this way our results confirm what is already known on the subject. In fact, to modify the arterial blood pressure in the systemic circulation the pulmonary vascular bed must be occluded to an extent varying from 41 to 90 per cent,[illegible] whereas Gibbon and colleagues[illegible] claimed that the area of the pulmonary artery must be reduced by 61 to 86 per cent, and Harrison and associates[illegible] did not obtain systemic hypotension even with ligation of the left pulmonary artery and the branches of the right pulmonary artery leading to the medial, inferior and accessory lobes (reduction corresponding to 85 per cent of the whole vascular pulmonary tree). Moreover most authors observed that not even the occlusion of a main branch of the pulmonary artery had any effect on the systemic arterial pressure.[illegible] Leusen and associates[illegible] alone obtained a slight increase in pressure in 4 of 9 cases, and Dotter and Lukas[illegible] observed a hypotension. Finally, Lewin and associates[illegible] observed systemic hypertension only when the balloon was inflated in the trunk of the pulmonary artery; there was no response if the balloon was inflated in the main branches of the pulmonary artery or in the right ventricle.

In our experiments, after occluding with the balloon a lobar branch of the left pulmonary artery, we injected distal to the balloon an embolus of barium sulfate and iron perchloride; although the embolus was injected into a vascular area already excluded from the circulation we obtained a further increase in pressure in the pulmonary artery, which was highly significant statistically. But more important, such an increase in pressure was far greater than the one evidenced by the previous inflation of the balloon, namely, 29.4 mm. Hg in the first instance and 3.6 mm. Hg in the second.

Before discussing the mechanism by which this embolization provokes such a hypertension, we have to exclude the possibility that the injected substance might have been disseminated over a vascular territory larger than the one into which it was injected. One of the objections made to lobar embolizations is that they really are much more extensive than the site of injection, mainly because some of the injected particles return and are dispersed afterward into a larger vascular territory.[illegible] However, in our experiments the embolus was injected distal to the occluding balloon, and Cate and associates[illegible] by histologic control showed that emboli injected distal to an occluding balloon are closely localized. Secondly, we ourselves carried out histologic controls which demonstrated that the injected barium could be found only in the pertinent lobe, and was entirely absent from the vessels of the other lung as well as other sections of the other lobes of the same lung (Figs. 2-4).

Another possibility is that some of the grains of the embolus might pass through the pulmonary capillary bed, reach the systemic circulation and be distributed to



Fig 3 Artery from the nonembolized lung (X120)

parenchyma the damaging of which would lead to serious consequences[12, 13] For instance because some areas of the hypothalamus have a regulating capacity on the lesser circulation[5, 14] it might be inferred that the arrival of embolic grains in these nervous centers would provoke as their electrical stimulation a pulmonary hypertension due to active vasoconstriction But first of all the addition of iron perchloride makes the suspension of barium sulfate clot immediately in the vessels into which it is introduced secondly its particles have an average size of 25 microns[16] and even admitting this like the grains of other substances they agglutinate as soon as they are in the blood circulation[15, 16] If one takes into consideration that only grains smaller in size than 2 microns will pass through the pulmonary capillaries and that they certainly will not pass if their size exceeds 8 microns[17] it is far too difficult to admit the possibility that the barium sulfate embolism will reach the left heart and then the systemic circulation Besides in the histologic examination carried out by Moore and associates[5] it was further confirmed that the injected barium sulfate collects in the arterioles and that it is only after vasodilatation by ganglion blocking agents that it can be diffused into the pulmonary capillaries Likewise in our own histologic examination we observed that the embolizing suspension plugs the arteries of the injected lobe but leaves the capillaries empty (Fig 4)

One more hypothesis has been mentioned in order to admit a larger circulatory obstruction than the one due to the first localization of the embolus namely a retrograde thrombosis formed beginning from the embolus itself and occluding also other proximal vessels[1, 19] But in our cases the inflated balloon was behind the embolus and it is impossible to imagine that the hypothetical retrograde thrombus could always be formed from the balloon contemporaneously—since the pulmonary hypertension started within a few seconds—with the barium sulfate embolization

To conclude we can accept as a demonstrated fact that the pulmonary hypertension in our cases was due to the injection of the embolic material exclusively



Fig 4 Artery from the embolized lobe (X120)

in this section of the vascular tree which had already been cut off from the circulation by the balloon. This hypertension was not retrograde in nature as it might have been had left ventricular failure developed with an increase in the pulmonary venous pressure. This we can be sure of because (1) the changes in pressure in the systemic circulation began after those occurring in the lesser circulation in all cases except two in which they were simultaneous (time correlation already seen by Halmagyi and associates[100]) (2) the pulmonary venous pressure did not increase at all and (3) the arteriovenous gradient as will be seen later rose rather than fell.

The lack of venous pulmonary hypertension excludes also the possibility that the latter may act through a reflex mechanism[106,107] on the pulmonary arterial pressure. On the other hand our observation of the absence of an increase in pressure in the pulmonary veins confirms the few determinations still being performed in the capillaries or in the pulmonary veins or in the left atrium[illegible]. Fabis[illegible] found a light hypotension in the veins. The contradictory data are few. Oppenheimer and associates[illegible] observed a venous hypertension in some cases of air embolism performed with the animal in certain positions whereas Singer and associates[illegible] recorded no changes in the left atrial pressure and hypertension in the pulmonary *capillaries but of moderate degree* and less than that found in the pulmonary artery anyway so that the gradient increased between artery and capillaries and between capillaries and veins.

The high increase in the arterial pressure on the one hand and the stability of the venous pressure on the other determined as a consequence of the embolization an increase in the pulmonary arteriovenous pressure gradient. At the time we did not record the pulmonary flow which is necessary for the determination of the pulmonary resistance but many investigators concur in pointing out that this either is reduced or remains unaltered by pulmonary embolization[illegible]. Hackel and associates[116] and Feruglio and associates[117] observed an increase in the cardiac output, but Hackel[116] showed that such an increase was inferior to that of the arteriovenous gradient owing to which fact the pulmonary resistance was increased. Thus we can state that the increase in the arteriovenous gradient which we observed means an increase in pulmonary vascular resistance.

It is obviously impossible to explain on an exclusively mechanical basis the pulmonary hypertension that we obtained and more precisely because the embolization—carried out in a branch already occluded by the balloon—in no way further reduced the vascular bed. For this reason one would assume in this case also the presence of a reflex mechanism provoking a generalized pulmonary vascular spasm which was shown by the increase in the pulmonary resistance.

Other investigators had already reached the same conclusions but by other methods of research. For such demonstration most of them used surgical or pharmacologic block of the various sections of the autonomous pulmonary system and obtained results showing both discrepancies and uncertainties[illegible]. Clearer results were obtained by Harrison and Moreau[illegible] with angiocardiography by Price and associates[illegible] on a heart lung head and denervated heart lung preparation and by Niden and Aviado[illegible] with crossed circulation. The factors which possibly may be able to stimulate the pulmonary receptors are[illegible] the rise in *the arteriolar pressure the mechanical* irritations in the vessels the hypotension distal to the segment of the artery occluded by the embolus and the release of chemical substances. Among the latter 5 hydroxytryptamine[illegible] histamine[illegible] and other unknown substances[illegible] have been either recognized or hypothesized.

Anoxia also was suggested by some workers as a vasoconstricting factor in the pulmonary embolization since an arterial oxygen desaturation was observed to follow it[illegible] and the anoxia itself was observed to have a remarkable power of pulmonary vasoconstriction[illegible]. But the role of anoxia in the pulmonary hypertension by embolization is not accepted by all authors. Actually it was demonstrated that no oxygen desaturation is obtained even after the occlusion of a main

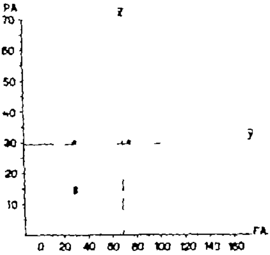


Fig 5 Abscissae Values of the drop in pressure in the femoral artery (mm Hg) Ordinates Values of the rise in pressure in the pulmonary artery (mm Hg) x and y Mean values of the changes in pressure respectively in the femoral artery and in the pulmonary artery

branch of the pulmonary artery that it is not in proportion to the pulmonary hypertension and finally that it follows instead of precedes the rise in pressure

Therefore these results also which were obtained by a method that in our opinion could exclude the mechanical factor in its determination make a positive contribution to the reflexogenic theory of the postembolic pulmonary hypertension

Also as for the severe systemic arterial hypotension observed by us after pulmonary embolization the most probable hypothesis is that it is due to a reflex mechanism This theory is supported by the same arguments as those already advanced for the genesis of pulmonary hypertension namely that the embolization after inflation of the balloon did not in any way determine a further reduction in the pulmonary vascular bed Anyhow if such a reduction were able to cause it systemic hypotension should also appear after occlusion of the lobar artery by the balloon but such a maneuver does not provoke any statistically significant change in the systemic blood pressure as was previously demonstrated

On the other hand the possibility and actual existence of pulmo systemic reflexes has been known since the investigations of Churchill and Cope and Schwiegk and has been confirmed many times

It is true that for those investigators who do not believe in the reflex genesis of the systemic hypotension the latter is due to the diminished venous return to the left atrium and to the reduced cardiac output and these features develop in effect after embolization with barium sulfate But if this were really the genesis of systemic hypotension we ought to register in individual cases a proportion between its value and that of the pulmonary arterial hypertension Such a relationship has not been recorded Rather we have had cases in which with a severe pulmonary hypertension there was a moderate systemic hypotension (for instance in Dog No 28) and vice versa (for instance in Dog No 37) The absence of correlation between the values for pulmonary hypertension and those for systemic hypotension – shown also by Parmley and associates and Osorio and Russek – is summarized in the scattergram of Fig 5 In Fig 5 the values for the rise in pulmonary arterial pressure were plotted for all individual cases against the values for the fall in femoral arterial pressure In this scattergram the values were not distributed in two opposite quadrants but equally in the four quadrants such a distribution shows that there is no correlation between the two values plotted We did not consider it to be necessary therefore to proceed with a determination of the correlation coefficient Neither did we observe any relationship between the values for systemic hypotension and the importance of the electrocardiographic feature This will be the subject of another report Thus with regard to the fall in systemic pressure after pulmonary embolization as well our research tend to conclude that it is due at least as a determining factor to a mechanism of a reflex nature

Summary

The purpose of this study on 25 closed chest anesthetized dogs which were subjected to catheterization of the pulmonar

arteries and veins was to contribute to the question of the nature of the pulmonary and systemic hemodynamic changes that occur with pulmonary embolization

By balloon occlusion of a lobar artery of the left lung a slight but statistically significant increase in the pulmonary arterial pressure and in the pulmonary resistance was obtained As with a simple mechanism of obstruction a similar rise in pressure was obtained—sometimes of lesser degree sometimes completely absent Only by occluding a main branch of the pulmonary artery we came to the conclusion that the hypertension which we have shown must also be based on the occurrence of a reflex factor

Inflation of the balloon led to no modification of either the pulmonary venous pressure or the systemic blood pressure

By successively injecting a suspension of barium sulfate and iron perchloride distal to the inflated balloon we obtained a further and much more severe increase in the pulmonary arterial pressure without a rise in the venous pressure and with an increase in the pulmonary vascular resistance Having ascertained also by histologic examination that the embolization could not be extended beyond the area of injection and so could not reduce the pulmonary vascular bed we confirmed that also for this remarkable hypertension in the lesser circulation the intervention of a reflex mechanism must be accepted

Together with the embolism a severe systemic arterial hypotension was obtained which was sometimes fatal We also have discussed the possibility of a reflex factor in the pathogenesis of this phenomenon

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The Polarcardiograph
Terminology and normal findings

*Gordon E. Dower, M.B.**
Heidi E. Horn
William G. Ziegler, B.Sc.
Vancouver, Canada

The Polarcardiograph described in detail in a previous paper[1] makes it possible to record at the bedside the spherical polar coordinates of the heart vector as continuous tracings. By recording as separate variables the magnitude and orientation of the electrical events associated with the heartbeat, a new and perhaps more fundamental picture is obtained.

When polarcardiograms employing only one polar axis are obtained, few difficulties in terminology are encountered. However, the use of three polar axes demands a more comprehensive terminology. Such a terminology should conform insofar as possible with that used in vectorcardiography and in standard engineering practice. Conventions in vectorcardiography have not yet become standardized, and several inconsistencies exist. For these reasons an account will be given of the various considerations involved in the setting up of a terminology for polarcardiography sufficiently inclusive to permit clear presentation of clinical material.[2]

Terminology

Coordinate systems. The relationship between rectangular (Cartesian) and spherical polar coordinates is shown in Fig. 1. Both are orthogonal coordinate systems in that their elemental vectors are orthogonal. An orthogonal coordinate system of three variables is either *left-handed* or *right-handed*. The right-handedness of the rectangular coordinate system illustrated in Fig. 1 is indicated by the following. If we imagine a right-handed screw to lie parallel with the Z axis, rotation of the head of the screw in the direction from X to Y will cause the screw to thread itself in a positive direction along the Z axis. A right-handed system cannot be transformed into a left-handed system by any rotation of the system as a whole. The spherical coordinate system illustrated in Fig. 1 is also right-handed insofar as it is conventional to consider the sequence of coordinates as R, θ, and ϕ, just as we consider the sequence to be X, Y, and Z in the case of Cartesian coordinates. It is usual practice for engineers to employ right-handed coordinate systems.

Use of a right-handed Cartesian coordinate system in vectorcardiography. There is general agreement in vectorcardiography concerning the direction of the X and Y axes (Fig. 1) and the orientation of the frontal and transverse views (Fig. 2). However, there seems to be a lack of agree

*From the [illegible] Hospital [illegible] the Department of Pharmacology, University of British Columbia, [illegible] British Columbia, Canada.

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Address: Department of Pharmacology, University of British Columbia, [illegible] B.C., Canada.

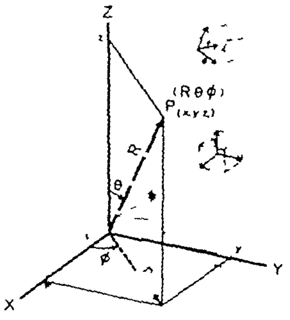


Fig 1 Relationship between rectangular and spherical coordinates as applied to the body The position P ... is described by (R θ φ) ... (x y z) Note that the ... increment ΔR Δθ and Δφ indicating the directions of the corresponding unit vectors are mutually orthogonal just as are the increments Δx Δy and Δz

ment as to whether the Z axis should point anteriorly or posteriorly [4,11] and whether the right or left sagittal view should be used Right handedness requires that the Z axis point posteriorly (Fig 1) The left sagittal view was preferred by the Committee on Standardization of Electrocardiographic and Vectorcardiographic Leads and Terminology called by the American Medical Association [1] Fortunately the combination of the posterior pointing Z axis and the left sagittal view permits consistency in the method of making angular measurements in each of the three views (Fig 2) difficulties such as noted by Helm[12] are avoided

Polar coordinates Two-dimensional polar coordinates are as old in electrocardiography as the use of Einthoven's triangle the electrical axis or Einthoven's angle α is approximately the angle of the heart vector in the frontal plane measured with respect to the X axis [13] We may following Abel [4] use β and γ in the transverse and sagittal planes respectively (Fig 2) This use of β has been made by other authors [14] The zero-degree reference and direction of making angular measurements—although not necessarily the scale 0 to ∓180—shown in Fig 2 have been used by several authors [7,10,11]

In deciding whether to measure angles in a plane on a 0° to 360 scale or on a 0 to ∓180° scale one can cite precedents for both methods Although the former method has been used by some authors [7,10,11] the use of the latter method for the frontal plane is traditional in the description of the electrical axis α and has been employed for the transverse and sagittal planes also [6,7,15]

Choice of polar axis A polar axis parallel to the Z axis yields the familiar frontal plane angle α This selection has been used by several workers [6] However some authors prefer a polar axis parallel to the Y axis [4,5] and clinical data indicate that polar axes parallel to the X Y and Z axes may be required [5] Polar axes parallel to the Y and X axes yield respectively β and γ and it becomes desirable to have a generic term analogous to polar angle to indicate the angle in the equatorial plane whether this be frontal transverse or sagittal

Latitude and longitude The term azimuth has been used to describe the angle in the equatorial plane Azimuth and elevation or altitude derive from a situation which has no analogy in the vectorcardiography they give the coordinates of a point with respect to an observer—the spherical polar coordinates of a star i e its right ascension and declination can be derived from its azimuth and elevation if the latitude of the observer and the date and time of the observation are known

When spherical representations and coordinates are used in describing the heart vector the terrestrial globe serves as a useful model in which the spherical coordinates latitude and longitude are familiar to everyone These terms have been used by several authors [4,5,6] Adopting longitude as a generic term we may speak of α as the frontal longitude β as the transverse longitude and γ as the sagittal longitude The corresponding latitudes are postero anterior PA inferosuperior IS and right left RL Thus the frontal longitude gives the direction of the heart vector in the frontal plane and the posteroanterior

latitude indicates the angle it makes posterior or anterior to this plane. The P A latitude has been termed the tilt by von der Groeben.

Latitude does not indicate the polar angle (θ Fig 1) but instead the angle measured with respect to the equatorial plane. The polar angle is the colatitude. There are advantages in using latitude rather than colatitude. In the first place latitude is more familiar; secondly the frontal, transverse and sagittal planes are more usual references in cardiology than their corresponding normals; and thirdly the use of colatitude raises the following problem of consistency. A colatitude scale has 90° at the equator, 0 at one pole and 180° at the other, so that if we orient the three polar axes to give a right handed system when α, β and γ measurements are made in the manner shown in Fig 2, we find that the 0° poles correspond to the −X, +Y and +Z directions respectively.

In a latitude scale 0 is at the equator and the poles are designated by 90° followed by P, A, I, S, R or L, which do not imply a polarity of the axis; thus the problem of consistency does not arise.

If we consider the frontal plane as the equatorial plane of our sphere, we can refer to latitudes as, for example, 10 anterior or 10°A just as we speak of a latitude of 10°S on earth. There is no need to keep the degree sign, and 10A can be interpreted as ten degrees anterior to the frontal plane. Similarly, employing the symbols P, A, I, S and R, L following a number of degrees, we indicate not only the direction but also the choice of polar axis. The symbols α, β and γ following longitudes also indicate the choice of polar axis.

Magnitude. The convention has been used of employing the symbols R and r to denote the spatial and equatorial plane magnitudes of a vector (Fig 1). Confusion

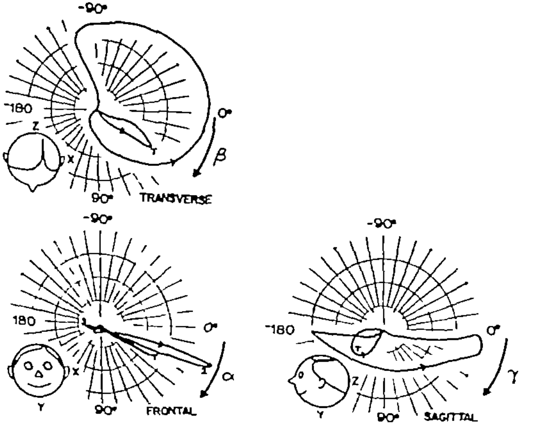


Fig 2 The terminology of angular measurements in the frontal, transverse and left sagittal planes. The vectorcardiographic loops were derived from the polarcardiograms in Fig 3

with their use in electrocardiography is avoided by replacing R and r with M and m Thus M fm tm and sm signify magnitudes in space and in the frontal transverse and sagittal planes respectively This permits us to use MR to indicate the spatial magnitude of the largest QRS vector and tmT to indicate the maximum magnitude of the T vector in the transverse plane and so on

Following the above mentioned convention it is useful to employ R and T to denote respectively the vectors associated with the R and T peaks in the spatial magnitude tracings

Thus we have three sets of symbols (P or A α fm M) (I or S β tm M) and (R or L γ sm M) according to which polar axis is used For example 60P +10α 0 9fm 1 8M indicates a heart vector described according to a postero anterior axis in which the latitude is 60° posterior to the frontal plane the longitude is +10 i e 10° from the X axis in a clockwise direction in the frontal plane the magnitude in the frontal plane is 0 9 unit and the spatial magnitude is 1 8 units Note that M is independent of the choice of axis and when different axes are used consecutively it can serve to identify corresponding complexes in a changing pattern

Polarcardiograms

1 DISPLAY OF ANGULAR COORDINATES AS TIME GRAPHS The Polarcardiograph makes it possible to obtain clinically time plots of the polar coordinates of the heart vector both in space and in a given plane (Fig 3) A suitable scale enables the angular coordinates of the heart vector at each instant to be read off For measurements of longitude the center of the scale reads zero and the extremities ∓180° There is a distinct advantage in choosing the scale to read downward from negative to positive values because it results in having the lower half of the scale correspond with the lower semicircle in the vectorcardiographic display This facilitates the correlation of vectorcardiographic loops with polarcardiograms Such a choice of scale gives polarities of polarcardiograms that conform with engineering practice even though we measure α in a clockwise direction This can be seen from the fact that if the longitude scale is inverted (but the galvanometer connections are unchanged) so that the positive values on the scale are uppermost the frontal transverse and sagittal angles then increase in a counterclockwise direction

The polarity of each latitude tracing is such that the heart vector in the corresponding vectorcardiographic display points into the screen when the tracing lies in the upper half of the scale The polarity of the latitude recording galvanometer corresponds with engineering practice right handedness and upwardly increasing scales

2 MAGNITUDE TRACINGS Although magnitude tracings resemble electrocardiograms they differ in that they possess no negative deflections Therefore it is meaningless to speak of Q or S deflections in these records However the P QRS and T events in the electrocardiogram have their clear counterparts Because the beginning and end of the deflections corresponding to the QRS interval in the electrocardiogram can be readily identified in the polarcardiogram (Fig 3) the term QRS interval may be retained Similarly we may employ P R and Q T intervals We may speak of the P wave the R wave the S T segment the T wave and the U wave In magnitude tracings the S T segment may be isoelectric or elevated but never depressed because there can be no negative magnitudes To avoid the conflict of referring to S T elevation in cases in which the electrocardiograms show general S T depression the term *S T displacement* is suggested

3 INTEGRATED SPATIAL MAGNITUDE It is often desirable to choose a single vector which may be considered to be representative of the QRS complex as for example in the definition of the electrical axis Naturally the first choice would be to take R̂ the vector associated with the peak of the R wave in the spatial magnitude tracing However in some cases this peak is ambiguous or may vary from beat to beat A second choice might be the vector occurring at the mid point in time of the QRS interval but the beginning and end of the interval are sometimes poorly defined and different interpreters could arrive at different mid points To avoid arbitrary decisions a representative QRS

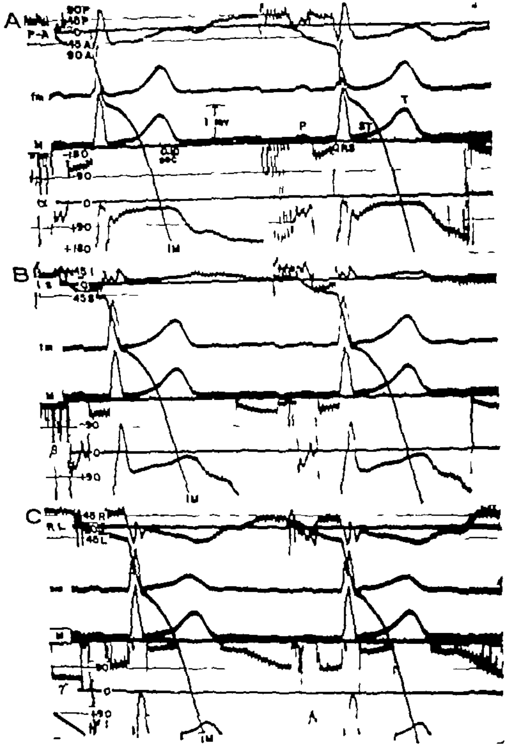


Fig. 3. Normal polarcardiograms based on a posteroanterior polar axis (A), an inferosuperior polar axis (B) and a right-left polar axis (C). P-A, I-S and R-L are latitudes and α, β and γ are longitudes. Magnitudes in the frontal, transverse and sagittal planes are labeled fm, tm and sm respectively. M is the spatial magnitude and is the same in all three tracings. The repetitive downsloping tracing IM is the integral of M.

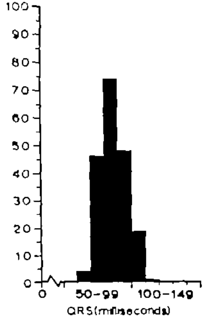


Fig 4 QRS intervals determined from spatial magnitude tracings of 192 subjects having normal electrocardiograms

vector is taken as that vector which occurs at the instant at which the area beneath the R wave in the spatial magnitude tracing is half its final value This point is readily obtained if the integral of the spatial magnitude is simultaneously recorded (*I M* Fig 3) Note that uncertainties as to the exact beginning and end of the QRS complexes have little consequence because their contribution to the total area under the R wave is small The vector occurring at the half area point we shall denote by ½R A corresponding vector ½T could be used to represent the T vectors although this has not been found to be necessary because the T peak is generally unambiguous

Normal findings

Method Polarcardiograms were obtained with the Polarcardiograph previously described[1] The x y and z input signals were obtained with Frank's lead system[20] Because patients were supine the chest electrodes were applied at the level of the fourth intercostal space[18] By means of switching of the input signals polarcardiograms were consecutively derived with respect to three polar axes viz P A I S and R L

Standard 12 lead electrocardiograms were obtained on the same day as the polarcardiograms Normal electrocardiograms were selected by showing the tracings to each of two experienced interpreters and asking them to indicate whether they were normal in all respects

The 2½ and 97½ percentile points were obtained from polarcardiographic data according to the method of Simonson[24]

The angle subtended by two vectors was obtained from their latitudes and longitudes by means of a table[7]

Results The population studied was composed largely of patients in a veterans hospital Since there were only 9 patients under 30 years of age and 4 women these were eliminated from the study There remained 192 men whose mean age was 58 6 years The age distribution was as follows where the number of cases in each age group is shown in parentheses 30 39 (17) 40 49 (40) 50 59 (39) 60 69 (51) 70 79 (36) 80 89 (10)

NORMAL POLARCARDIOGRAM A typical normal polarcardiogram is illustrated in Fig 3 In Fig 3 *A* the polarcardiogram was taken using a posteroanterior axis as the polar axis The latitude tracing gives the angle with respect to the frontal plane either posterior or anterior The longitude angle is the frontal angle and corresponds to Einthoven's angle α Of the two magnitude scales one is the spatial magnitude and the other is the frontal magnitude

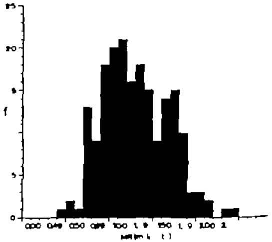


Fig 5 1 Frequency distribution of MR in 192 subjects with normal electrocardiograms

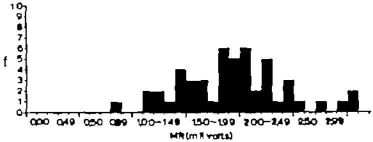


Fig. 5B Frequency distribution of MR in 50 athletes



Fig. 5C Frequency distribution of MT in 19 subjects with normal electrocardiograms

i.e. the projection of the spatial magnitude on the frontal plane. The down step of the base line preceding the P wave of the second beat is caused by an automatic clamp which defines the origin of the coordinate system at each beat, thus compensating for base line drift in any of the x, y or z signals fed to the computer. The polarcardiogram from the same patient obtained using an inferosuperior axis as the polar axis is shown in Fig. 3 B. In this case the latitude is the angle of the heart vector below or above the transverse plane and the longitude is the transverse angle β. The transverse magnitude is the projection of the spatial magnitude on the transverse plane. The spatial magnitude tracing is identical with that shown in Fig. 3 A. In Fig. 3 C the polarcardiogram obtained using a right to left axis as the polar axis is illustrated. The latitude gives the angle to the right or to the left of the sagittal plane whereas the longitude gives the sagittal angle γ. The sagittal magnitude is the projection of the spatial magnitude on the sagittal plane. The spatial magnitude is identical with that shown in A and B of Fig. 3. The repetitive down sloping tracing (IM, Fig. 3) represents the integral of the spatial magnitude curve and serves to define IR, giving a typical direction for the QRS vectors. The integrator is reset by the clamp pulse. Vectorcardiograms from the same patient are shown in Fig. 2. Note that a counterclock

Fig. 5D Frequency distribution of MT/MR in 19 subjects with normal electrocardiograms

wise direction of rotation of the loop is indicated by an upslope in the corresponding longitude tracing of the polarcardiogram. The vectorcardiograms in Fig. 2 were plotted from the polarcardiograms in Fig. 3. Although this is a somewhat tedious means of obtaining vectorcardiograms and indeed represents a procedure which is not normally necessary, it serves here to illustrate the relationship between the two types of records. The procedure has some merit, however, because polarcardiograms, being displayed on a time scale, make it possible to select a typical heart cycle and thus to derive typical vectorcardiograms. Furthermore, ambiguity of the vectorcardiogram close to the origin is avoided when such a derivation is made.

DURATION OF THE QRS INTERVAL. By means of the spatial magnitude curve of the polarcardiogram it is a simple matter to obtain accurate measurements of the duration of the QRS interval. Unlike an electrocardiogram, in which part of the QRS complex may be isoelectric, a zero value of the spatial magnitude indicates that *all* heart vectors are zero; hence, the beginning and end of the QRS interval on the spatial magnitude tracing accurately indicate the beginning and end of the ventricular activation cycle and the generation of vectors associated with it. Furthermore, the fivefold increase in paper speed over that commonly used in electrocardiography renders a further improvement in the accuracy of this interval measurement. In some individuals in whom the onset of ventricular activation appears to be very gradual, identification of the beginning of the QRS interval may be difficult. However, in these cases similar or greater difficulties would exist for corresponding electrocardiographic measurements.

The frequency distribution of spatial magnitude QRS intervals in 192 patients whose electrocardiograms were normal is shown in Fig. 4. The lower and upper 2½ percentile points, encompassing 95 per cent of the population studied, lie at 61 and 105 msec., respectively.

SPATIAL MAGNITUDE OF MAXIMUM QRS AND T VECTORS AND THE RATIO BETWEEN THEM. The spatial magnitude of $\hat{R}$, MR, is directly dependent on the choice of lead system and the scaling factor contained in it. The units on the scale employed are those corresponding to the amplitude of the spatial magnitude deflection resulting from the injection of a 1 mv. calibration signal into any one of the coordinate inputs X, Y, or Z.

The frequency distribution of MR in 192 patients whose electrocardiograms were normal is illustrated in Fig. 5A. This suggests that 2.0 mv. may be considered to be an upper bound of normality—the lower and upper 2½ percentile points are 0.69 and 2.03 mv., respectively. For comparison, the frequency distribution of MR in 50 athletes is shown in Fig. 5B. In this group there is a considerable shift of the MR distribution to the right. The average age of this group, 20.1 years, was considerably below that of the group in Fig. 5A, and this factor alone could be responsible for larger values of MR. Voltages tend, of course, to be greater in the electrocardiograms of young people,[8] but it is possible that athletic training was also responsible for the increase in the amplitude, presumably because of physiologic hypertrophy.[9]

The spatial magnitude of T, MT, in 192 patients has the frequency distribution shown in Fig. 5C. The scatter is somewhat less than that of MR—the lower and upper 2½ percentile points are 0.193 and 0.744 mv., respectively. Fig. 5D shows the frequency distribution of MT/MR in the same population. The lower and upper 2½ percentile points are 0.141 and 0.604, respectively.

SPATIAL DIRECTION OF MAXIMUM QRS AND T VECTORS AND THE ANGLE BETWEEN THEM. The polarcardiogram immediately provides the spatial directions of the P, QRS, ST, and T vectors. These may be plotted on the surface of the globe or, more conveniently, on an equal-area projection.[11] An equal-area projection is preferable to, say, a Mercator projection because account must be taken of the crowding together of longitude coordinates at the poles. A uniform distribution of points on the surface of the sphere when plotted on a Mercator projection would result in an apparent increase in density at the equator at the expense of the poles. Transferring data to Aitoff's equal-area projection avoids this difficulty, so that a distri-

bution which appears to be uniform on a sphere appears to be uniform on this projection. Fig. 6*A* shows the directions of R in 184 of the 192 cases with normal electrocardiograms—there were 8 cases in which double peaks in the spatial magnitude tracing made the determination of R ambiguous. The vector IR is never ambiguous. Its direction is plotted in the 34 cases in which the integral of the spatial magnitude curve was recorded (Fig. 6*B*). Generally, the $\hat{R}$ and $\hat{IR}$ plots cover a wide expanse; however, certain generalizations can be made. Anterior to latitude 50P the distribution tends to fall between longitudes −20α and +90α. There are no cases showing $\hat{R}$ directed anteriorly to latitude 40A. This leaves about two thirds of the area of the globe unoccupied. IR plots appear to have roughly the same distribution as $\hat{R}$ plots.

The distribution of T directions in the 192 cases (Fig. 6*C*) has much less scatter than that of R and IR, since 95 per cent are contained in one fifteenth of the area of the globe. It is almost entirely anterior and lies between longitudes 0α and +80α. Note that a direction of 15A, +15α would be within the latitude and longitude ranges for T but represent a position on the globe not occupied by any of the 192 cases. This illustrates the importance of considering both variables together.

The frequency distribution of the spatial angle between R and for the 184 cases in which R was not ambiguous is shown in Fig. 6*D*. The scatter almost covers the full range from 0 to 180°. The 2½ and 97½ percentile points are at 13.2° and 149.6°, respectively.

Discussion

An analogue device described by Abildskov and co-workers[19] is directly comparable to the Polarcardiograph. Pipberger and associates[21] and Toole and associates[1, 2] have employed digital computers to give similar readouts. Our experience with α, β and γ polarcardiograms dates from 1955 when a two-dimensional model was used on 40 patients.[22]

The need for three sets of polarcardiograms derived from the X, Y and Z polar axes appears to conflict with the fact that the heart vector at any instant is completely defined by any one set of three orthogonal coordinates. If the problem were one merely of definition, the transformation from Cartesian to polar coordinates would not be necessary, since it adds no new information. The role of the Polarcardiograph is to provide a different display of the information present in the X, Y and Z signals derived from the patient. By this means significant variations not previously apparent may be brought to light. The initial choice of a postero-anterior polar axis was made because it provided, in the α tracing, a continuous record of the electrical axis. But because of the fact that the frontal view tends to see the QRS loop end on, the direction of rotation and, therefore, the α tracing are quite variable. On the other hand, the transverse and sagittal views are relatively consistent—and it would be expected that distortions of polarcardiograms due to infarction would be more obvious in the β and γ tracings. This has been found to be the case.[3] However, for the presentation of numerical data of the type given in Figs. 4-6, posteroanterior polarcardiograms are sufficient and, for simplicity, all such data are given in terms of these coordinates.

The selection of representative or typical QRS vectors from vectorcardiographic loops presents several problems. Despite modulation of the beam, accurate timing cannot be achieved by the vectorcardiogram alone.[24] Furthermore, the apparent beginning of QRS loops may be asynchronous in different views, so that the 0.02 second vector in the frontal plane, for example, may not be identical with a similarly identified vector in the transverse plane. The polarcardiogram makes accurate timing and the correct spatial orientation of vectors possible. The duration of the QRS interval is usually clearly indicated, but although its termination is seldom in doubt, the beginning of ventricular activation is occasionally rendered ambiguous by a small initial deflection or foot which varies from case to case from being clearly discernible to conjectural. One would conclude from this that the onset of the electrical field associated with ventricular activation can be very gradual. The existence of a foot, even when readily

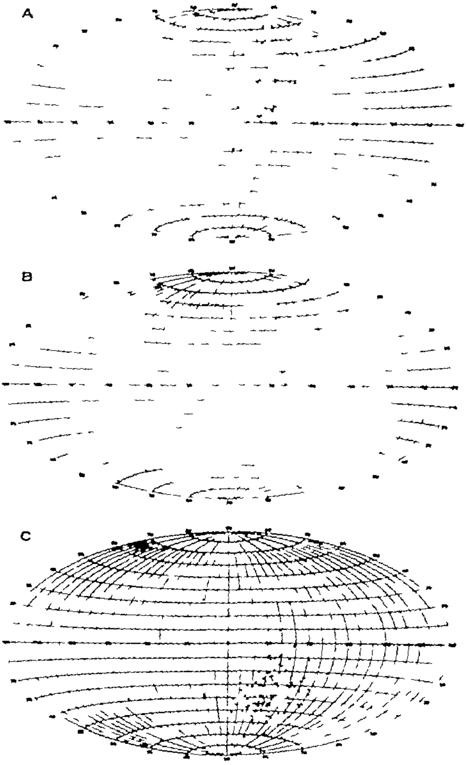


Fig. 6A. Directions of R in 184 subjects with normal electrocardiogram

Fig. 6B. Directions of 1R in 34 subjects with normal electrocardiogram

Fig. 6C. Directions of 1 in 19? subjects with normal electrocardiogram

discernible raises a problem in comparison For example the spatial magnitude in one case might show a foot resulting in a total QRS duration of 0 08 second but another case with otherwise very similar tracings may not have this feature and have a QRS duration of 0 07 second One would infer that apart from the foot the electrical fields occurring in these two cases are very much alike and one might say of the foot that it represents a small early localized region of activation but does not bespeak a major difference in the over all pattern of activation However if the electrical events are compared by taking samples every 0 01 second after the commencement of activation [34] the general similarity will be obscured since all measurements in one case will be advanced by a time equal to the duration of the foot

With respect to the problem of defining a single vector which may be considered to be representative of the QRS vectors the adoption of the vector occurring at the mid point of the QRS interval is subject to the type of error mentioned above and the selection of the vector associated with the peak value of the spatial magnitude tracing is unsatisfactory when there are two peaks of almost equal size The use of IR the vector at the half area point of the R wave in the spatial magnitude tracing avoids these difficulties ĪR should not be confused with the spatial QRS area vector which is derived from the electrocardiogram by a means similar to that employed for the spatial ventricular gradient and which is of course yet another parameter that can be considered to be representative of the QRS vectors [37] The spatial ventricular gradient can be obtained by electronic means but has doubtful theoretical advantage [38]

The polar vector of Burger and Vaane[39] is an elegant and useful[40] solution to the problem of finding a representative QRS vector but like the determination of the half area vector of Pipberger [41 42] involves planimetry of loops It should be pointed out however that measurements of the areas of loops take no account of variations in the time course of the unfolding of electrical events This is illustrated in Fig 7 which shows two loops of similar shape having very different rates of inscription These differences are manifest in the corresponding magnitude tracings and would thus be taken into account by IR

It is of interest that the QRS duration obtained by means of the spatial magnitude tracing is somewhat shorter than that derived by very careful measurements of the electrocardiogram [illegible] The discrepancies appear to be due to difficulty in defining the end of the QRS complex in precordial leads Lepeschkin and Surawicz[illegible] defined the end of the QRS complex in such a way that the isoelectric point preceded the point taken as the end of the interval A similar comment applies to the method of Blackburn and Simonson [illegible] However the spatial magnitude tracing indicates that we should take the nadir at the end of the QRS complex to signify the termination of the interval In general in the normal spatial magnitude tracing this demarcation turns out to be quite clear (Fig 3) The spatial magnitude is usually zero at the end of the QRS complex in normal tracings and the electrocardiogram must be isoelectric at this time Hence measurements of QRS intervals in the manner described above would include some of the S T segment

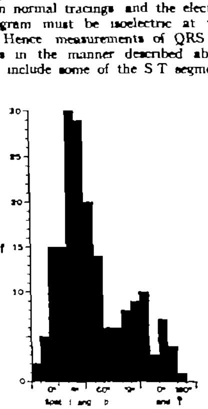


Fig *6D* Distribution of spatial angle between peak QRS and T vectors

The spatial magnitude tracing is valuable in providing an index of the maximum QRS vector irrespective of direction. The diagnosis of left ventricular hypertrophy from the electrocardiogram is largely based on the observation of large amplitude QRS complexes.[11,14] These are considerably dependent on heart position, and one can visualize cases in which, although the maximum QRS vectors in space are of large magnitude, their direction is such that they do not give rise to particularly large complexes in the electrocardiogram. It would be expected on these grounds that MR might serve as a useful indication of ventricular enlargement.

The usefulness of MT remains to be determined. The normality of T waves in the electrocardiogram is judged partly on the proportion of their amplitudes to QRS amplitudes. This leads to the expectation that the frequency distribution of MT/MR would show less scatter than that of MT.

The rather widespread distribution of R directions—which cover approximately one third of the globe—suggests that expectations as to the usefulness of the direction of R in a definition of normality should be modest. On the other hand, the fact that 95 per cent of T directions cover an area which is only one fifteenth of the global surface encourages the view that the spatial direction of T may provide a sensitive indicator of normality. The wide range of values for the spatial angle between R and T is disappointing because it indicates that this would not be a useful measure of normality, although it may still prove to be useful in distinguishing one clinical condition from another.

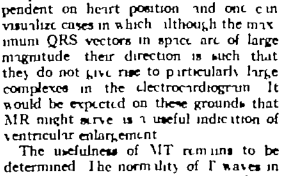


Fig. 7. Two hypothetical transverse loops having similar shapes. The total durations of inscription are the same for both, but the early part of the left-hand loop and the terminal part of the right-hand loop show delay. This is indicated by crowding of the dots, which are at 0.004 second intervals. It is also revealed in the transverse tracings (*tm*). The vectors ĪR occur at the time the magnitude tracings are half inscribed with respect to areas beneath the curves. For the purpose of illustration, ĪR has been derived from the transverse magnitude instead of the spatial magnitude. The dotted arrows are the half-area vectors derived from planimetry of the loops. These depend only on the shape of the loops and are thus the same for both, whereas the vectors ĪR indicate that the unfolding of the electrical events is different in the two cases.

Summary

The clinical application of the Polarcardiograph has brought out the need for a comprehensive yet concise terminology to describe the polar coordinates of the heart vector. In the terminology proposed, precedent has been followed insofar as consistency and clarity permit.

Frontal, transverse, and sagittal longitudes designated by α, β, and γ have been based on Einthoven's precedent for α. The corresponding latitudes are indicated by P, A, I, S, and R, L. The spatial magnitude is indicated by M, and the magnitudes in the frontal, transverse, and sagittal planes by fm, tm, and sm. By integration of the spatial magnitude tracing produced by the QRS vectors, a point is found at which the area under this curve is half inscribed. The QRS vector associated with this point in time is termed IR. It is suggested that this be considered representative of the QRS vectors. Other defined vectors are R, the peak QRS vector, and T, the peak T vector.

The usefulness of the Polarcardiograph derives from the fact that it provides a fresh display of the electrical events associated with the cardiac cycle. P-R, QRS, and Q-T intervals are clearly indicated by the spatial magnitude tracing and have their usual significance. However, difficulties arising out of asynchronous isoelectric portions of the electrocardiogram are avoided.

In a group of 192 elderly men with completely normal electrocardiograms, the QRS interval determined from the spatial magnitude tracing was found to be between 61 and 105 msec. for 95 per cent of them. The distributions of values for the spherical polar coordinates of R and T

are given The relationship between R and T was indicated by the distribution of their magnitude ratio MT/MR and of the subtended angle

The spatial magnitude of R MR was between 0 7 and 2 0 mv in 95 per cent of the cases (A small sample of athletes showed much larger values) The spatial magnitude of T MT was between 0 19 and 0 74 mv The directions of R covered approximately one third of the globe s surface Most remarkable was the relatively small scatter of the directions of T of which 95 per cent were contained in one fifteenth of the globe s surface

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The Polarcardiograph
Diagnosis of myocardial infarction

*Gordon E. Dower, M.B.**
Heidi E. Horn
William G. Ziegler, B.Sc.
Vancouver, Canada

The Polarcardiograph has been described in detail in a previous paper.[1] With this device it is possible to record at the bedside the spherical polar coordinates of the heart vector as continuous tracings. Tracings were obtained in approximately 40 normal individuals in 1955 using a two-dimensional version, but an extensive clinical trial of the method had to await the development of the more refined version.

Clinical trial of the Polarcardiograph began in 1961, and over 2,000 recordings have been taken. Because the appearance of the records obtained is quite different from conventional electrocardiograms (ECGs) or vectorcardiograms (VCGs), a system of interpretation had to be worked out. This has now been done for some of the common conditions recognized in the ECG. The present paper describes five simple diagnostic criteria which have been found to be useful in the diagnosis of myocardial infarction, and presents a quantitative evaluation of these criteria.

Method

Polarcardiograms (PCGs) were recorded using Frank's lead system, with the modification of applying the chest electrodes at the level of the fourth intercostal space anteriorly when the patient is in the supine position.[2] ECGs were obtained on the same day as the PCGs.

The population studied was composed largely of patients in a veterans' hospital. When patients gave histories of myocardial infarction elsewhere, attempts were made to obtain tracings from other hospitals. With few exceptions, all autopsies were witnessed by one or more of the authors, and, in general, the hearts were cut in transverse slices—"bread loafing."

The following methods of handling data were used: PCGs and copies of all relevant ECGs were filed together under the patient's name. The interpretation and comments were entered on punch-cards. All PCGs were photographed on 35 mm. film, and 5 by 7 cm. prints were placed in an album according to diagnosis. Autopsy reports, when available, were filed with the PCGs and ECGs, and an entry was made in a notebook and on punch-cards. By means of the latter it was possible, for example, to make a selection of all patients having a QRS interval greater than a prescribed amount, a peak QRS vector lying in a particular magnitude range, a T vector with a particular spatial

*From the [illegible] Department of Pharmacology, University of British Columbia, Vancouver, British Columbia, Canada.

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Address: Department of Pharmacology, University of British Columbia, Vancouver 8, B.C., Canada.

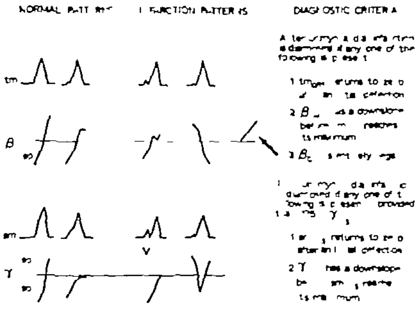


Fig 1 The polarcardiographic diagnostic criteria

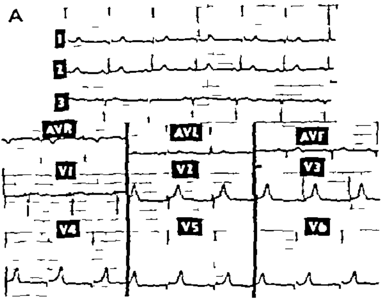


Fig 2 The ECG appears normal (*A*) but the PCG indicates AMI by $tm_{QRS} \to 0$ (*B arrow*) AMI is confirmed by the ECG taken 8 years earlier (*C*) *D* Transverse VCG loop drawn from *B* note return to origin between parts *1* and *2* of the QRS loop The P loop is not shown The return of the base line to zero after the T wave in the magnitude tracings (*tm* and *M* in *B*) is caused by the base line clamp (*see text*) (For *B C* and *D* see opposite page)

direction etc. The album made it possible to compare configurational details in PCGs in any one patient with those in all other patients. The time required for such a comparison was usually about 20 minutes

Results

Diagnostic criteria for myocardial infarction The polarcardiographic display describes the heart vector at any instant in terms of its magnitude and its direction

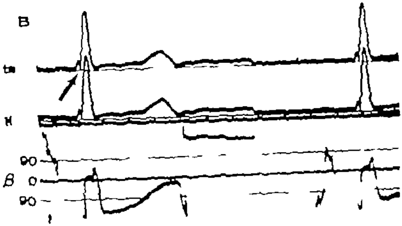


Fig 2B

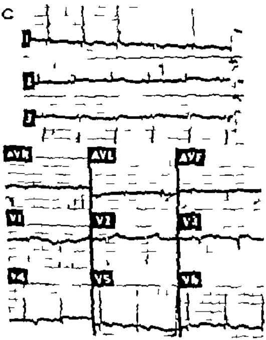


Fig 2C

which is defined by two angles latitude and longitude The reference axis or polar axis is conveniently chosen parallel to the X Y or Z axes employed in vectorcardiography which run respectively from right to left superior to inferior and anterior to posterior When the reference axis is parallel to the Z axis the longitude becomes synonymous with Einthoven's angle α in the frontal plane In the transverse and left sagittal planes the corresponding transverse and sagittal longitudes are termed β and γ In addition to the spatial magnitude the magnitude of the heart vector in space the Polarcardiograph yields the magnitudes in the frontal transverse and sagittal planes The diagnostic criteria to be described for myocardial infarction apply only to the transverse magnitude tm the transverse longitude β the sagittal magnitude sm and the sagittal longitude γ When these symbols relate to QRS events they are written tm_{QRS} β_{QRS} sm_{QRS} and γ_{QRS} respectively

It is convenient to divide all cases of myocardial infarction into anterior and

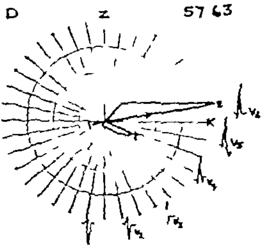


Fig 2D

inferior infarction. *Anterior myocardial infarction* (AMI) is indicated by abnormalities in tm_{QRS} and/or β_{QR} (Fig. 1). Any one of the following signs is sufficient to diagnose AMI: (1) an initial deflection in tm_{QRS} which returns to zero before the main part of the tm_{QRS} curve is traced, (2) a downslope in β_{QR} at any time before tm_{QRS} reaches its maximum, or (3) β_{QR} negative throughout. *Inferior myocardial infarction* (IMI) is indicated by abnormalities in am_{QRS} and/or γ_{QR} (Fig. 1). Subject to the proviso that γ_{QR} is initially in the range −170 to −45°, either of the following signs is sufficient to diagnose IMI: (1) an initial deflection in am_{QR} which returns to zero before the main part of the am_{QRS} curve is traced, or (2) a downslope in γ_{QRS} before am_{QR} reaches its maximum.

Illustrative cases

The above-mentioned criteria may yield a diagnosis of myocardial infarction even when the ECG recorded at the same time appears to be normal (Fig. 2A). In this example, AMI is indicated in the PCG (Fig. 2B) by tm_{QR} returning to zero after an initial deflection, and the ECG recorded 8 years earlier (Fig. 2C) indicates that an AMI had in fact occurred. For the purpose of later discussion, the corresponding VCG loop (Fig. 2D) was constructed from the tm and β tracings. The feature of the loop which corresponds to the initial deflection of tm_{QRS} is the component directed anteriorly and to the left (labeled *1* in Fig. 2D). This returns to the origin before the main part of the QRS loop is written.

The ECG in Fig. 3A suggests IMI and that taken 1 year earlier confirms it (Fig. 3B). In this case the diagnosis is indicated in the PCG (Fig. 3C) by am_{QRS} returning to zero after an initial deflection and a downslope in the γ_{QRS} tracing.

The ECG in Fig. 4A indicates anteroseptal myocardial infarction. There is no sign of the IMI which appears in the ECG taken 13 years earlier (Fig. 4B). In this case four diagnostic criteria are present in the PCG (Fig. 4C: $tm_{QR} \to 0$, $\beta_{QRS} \downarrow$, AMI, and Fig. 4D: $am_{QR} \to 0$, $\gamma_{QR} \downarrow$, IMI).

The ECG in Fig. 5A is the sort of ECG that often causes difficulty in interpretation. It suggests AMI but not IMI. However, the ECG 2 years before shows IMI (Fig. 5B). The PCG indicates IMI (Fig.

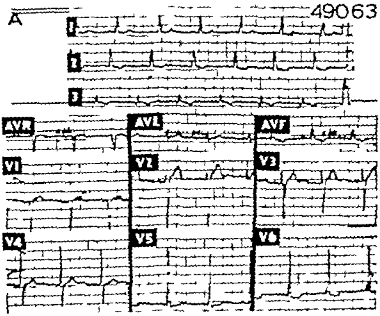


Fig. 3. The ECG suggests IMI (A), which is confirmed by the ECG taken 1 year earlier (B). The PCG taken with A indicates IMI by $am_{QRS} \to 0$ and $\gamma_{QRS} \downarrow$ (C, arrows). (For B and C see opposite page.)

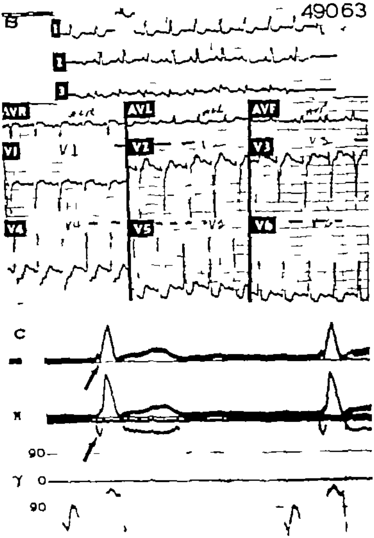


Fig 5B ... (For ... pat)

5C $\epsilon m_{QRS} \to 0$ γ_{QR} ↓) and AMI (Fig 5D $t m_{QRS} \to 0$ β_{QR} ↓) Both infarctions were confirmed at autopsy 6 weeks later

The ECG in Fig 6A indicates anterior subendocardial infarction In this case the PCG indicates AMI (Fig 6B $tm_{QR} \to 0$ β_{QRS} ↓)

Quantitative comparison between diagnostic performances of PCG using criteria given and of ECG using standard criteria

Method An unbiased quantitative appraisal was made of the diagnoses based on the polarcardiographic criteria for myocardial infarction (PCCA) compared with an independent diagnosis based on the ECG The ECG recorded when the PCC was taken was shown separately to each of two interpreters who were given no other information The interpreters had wide experience They tended to think vectorcardiographically and in general to agree with one another They showed impressive consistency in their interpretation of difficult tracings Conventional diagnostic criteria were employed

The interpreters indicated their diagnoses according to a questionnaire (Table I) A graded response to the first three questions was permitted viz definitely probably possibly and no It was thought that this kind of answer imposed no restraint on the diagnosis A

A

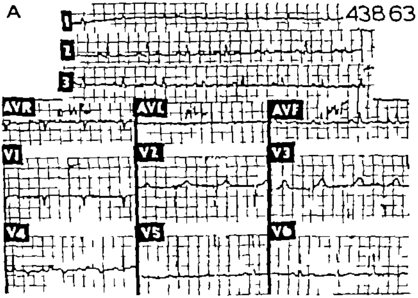


Fig 4 The ECG suggests anteroseptal infarction (A) but not IMI which was visible in the ECG taken 13 years earlier (*B*) The PCG taken with A indicates AMI by $tm_{QRS} \to 0$ and $\beta_{QRS} \downarrow$ (*C arrows*) and IMI by $\alpha m_{QRS} \to 0$ and γ_{QRS} (*D arrows*) (For *B* *C* and *D* see opposite page)

conversion of their answers to Question 3 into the yes or no type of answer which the PCG criteria give was carried out as follows Definitely and probably were taken to indicate probably yes whereas possibly and no were taken to mean probably no When both readers answered probably yes this was considered to be affirmative or positive and when both answered probably no this was considered to be negative combinations of probably yes and probably no were considered to be doubtful The diagnosis thus obtained was termed the ECG diagnosis (ECG Δ)

Each case in which the PCGΔ and ECGΔ were different was reviewed by the two interpreters together They were given all relevant information available including ECGs but they were not aware of the PCGΔ or that it differed from the ECGΔ Acting in concert the interpreters thus reached the best diagnosis (BestΔ) When opinion was divided the BestΔ was considered to be doubtful The BestΔ could differ from the ECGΔ only when significant additional material in the form of previous ECGs or autopsy evidence was available Because the value of the ECG in the diagnosis of myocardial infarction was not at issue and it was of interest merely to establish whether the PCG was more or less useful cases in which there was exact agreement between the ECGΔ and PCGΔ were not further studied In these the ECGΔ and BestΔ were considered to be identical

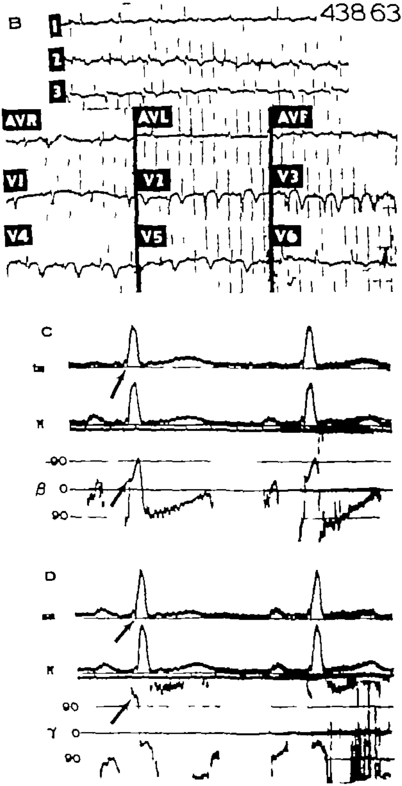
Results The significance of tm β am and γ in the diagnosis of myocardial infarction was not initially realized so that out of a total of approximately 2 000 PCG records 1 000 have tm and β tracings and only 500 have in addition am and γ

Table I Questionnaire for reading ECGs for PCG evaluation in myocardial infarction

Readings to be based on examination of single ECGs without knowledge of clinical picture or age

Questions

1 Is tracing normal in all respects?
2 Is QRS normal?
3 Would you diagnose MI on this tracing?
4 What is/are the location(s)?
5 Indicate whether AMI IMI or both is the best alternative description
6 What is the type of infarction?
7 What is the age?


B
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I
II
III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6
C
-90
β 0
90
D
90
γ 0
90

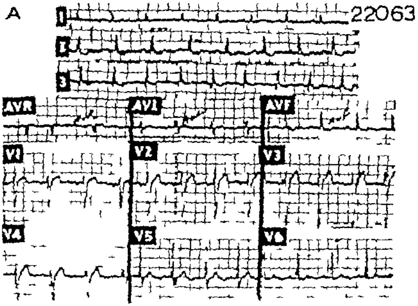


Fig. 3. The ECG suggests AMI (A) but not PMI, which was visible in the ECG taken 1 year earlier (B). The PCG taken with the ECG indicates PMI by tmax → 0 and run ↓ (C arrows) and AMI by tmax → 0 and dur ↓ (D arrows). Both infarctions were confirmed at autopsy. (For B-D see p. 377.)

tracings. The present results are concerned only with the cases having both of these pairs of records. When a patient had PCGs taken on more than one occasion, only one was used, unless significant changes had taken place in the interval. Ten patients under the age of 30 were eliminated to make the age range of the population conform with that of a normal population studied.[3] The patients' ages had an arithmetic mean of 66.4 years, and the distribution was as follows, where the number of patients in each age group is shown in parentheses: 30-39 (20), 40-49 (43), 50-59 (63), 60-69 (133), 70-79 (174), 80-89 (58), 90 and over (2). There were only 2 female patients.

A comparison between the PCGΔ, the ECGΔ, and the BestΔ is shown in Table II. In the group of 493 cases, the PCGΔ was positive for myocardial infarction in 294, negative in 190, and ambiguous in 9. The ambiguity derived from very small abnormalities associated with muscle tremor. Out of the 294 cases in which the PCGΔ was positive, the ECGΔ was positive in only 146, but when more information was provided about many of these cases, agreement with the PCGΔ improved: the BestΔ was positive for 215 cases. Thus, there is a trend toward the PCGΔ of 69 cases. This improvement in agreement results from a reduction in the number of cases in which the ECGΔ was negative or doubtful. When the PCGΔ was negative, there were only 3 cases in which the ECGΔ was positive, and these were all cases of subendocardial

Table II. Diagnosis of myocardial infarction (out of 493 cases). Polarcardiographic diagnosis (PCGΔ) vs. diagnosis from single ECG (ECGΔ) and from all ECGs and postmortem data (Best Δ) (where relevant)

		PCG Δ +	PCG Δ −	PCG Δ ?
ECG Δ	+	146	3*	1
	−	92	173	7
	?	56	14	1
		294	190	9
BEST Δ	+	215	10	2
	−	57	174	7
	?	22	6	0
		294	190	9

*All subendocardial infarcts.

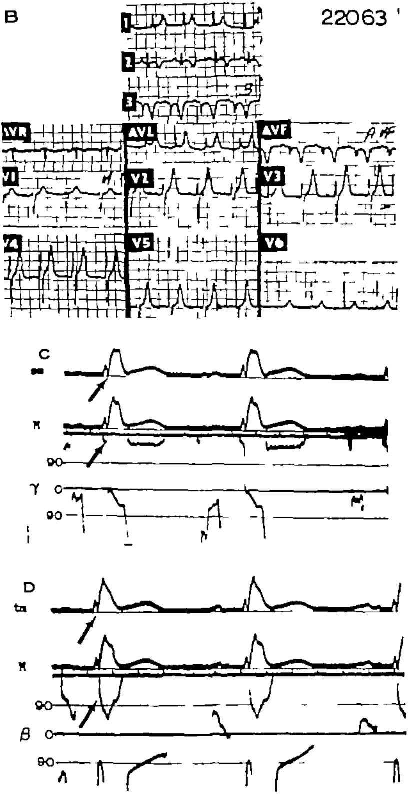


Fig 5 B C and D (For l ...)

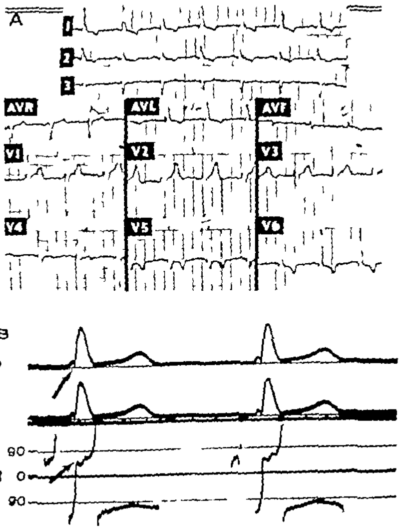


Fig. 4. The ECG indicates anterior subendocardial infarction (A). The VCG indicates AMI by $\beta_{max} \rightarrow 0$ and $\beta_{QRS} \downarrow$ (B, arrows).

infarction. No distinction between subendocardial and transmural infarction is made in Table II. It turned out that in the 493 cases there were 21 in which the ECGΔ was subendocardial infarction, that is, the diagnosis was not based on the QRS complex. *Although the VCG criteria relate only to the QRS complex,* the diagnosis of myocardial infarction was made in 18 of these cases. There were only 9 cases in which the VCGΔ was doubtful, whereas there were *71 cases in which the ECGΔ* was doubtful—a figure which was reduced to 28 in the BestΔ when more information was provided.

In some cases a diagnosis of both AMI and IMI was made on the basis of the VCG criteria, whereas the ECGΔ or the BestΔ indicated either one of these. Agreement as to location in these cases was considered to be partial. Agreement with the VCGΔ was partial in 49 for the ECGΔ and in 45 for the BestΔ. Probably several cases which are *labeled AMI have infarctions* extending inferiorly, and the significance of only partial agreement as to location is probably not great. In a few cases the diagnosis of IMI was made in *the VCGΔ but the diagnosis of AMI* was made in the ECGΔ or BestΔ. There were 4 such cases for the ECGΔ and 8 for the BestΔ. There was complete agreement as to location in 93 cases with the ECGΔ and in 162 cases with the BestΔ (Table III).

The ECGΔ and BestΔ each differed from the PCGΔ as to location of infarction in 53 cases Agreement as to whether or not an infarction had occurred existed in 319 cases (64 7 per cent) with the ECGΔ and in 389 cases (78 9 per cent) with the BestΔ There is clearly a trend toward agreement with the PCGΔ An exact coincidence between the BestΔ and PCGΔ would not be expected in this series because in many cases earlier ECGs were not available and even though there may have been a history suggestive of myocardial infarction the absence of ECG or autopsy evidence precluded any change being made when the BestΔ was obtained

Another way of evaluating the performance of the PCG criteria is to study false positives and false negatives A diagnosis of previous myocardial infarction can often be made on the basis of previous ECGs so that the occurrence of false negatives in the PCGΔ should be relatively easy to detect Table IV indicates that based on the BestΔ the number of false negatives was 10 or 2 per cent All these cases had subendocardial infarctions It is fairer however to compare the PCGΔ with the ECGΔ which results in only 3 false negatives or 0 6 per cent These had subendocardial infarctions False positives are harder to establish than false negatives since only a subsequent negative postmortem examination of the heart can exclude infarction However even at autopsy infarctions can be missed unless considerable care is taken in sectioning the heart If we base the PCG false positives on the ECGΔ (Table IV) we find that there were 92 cases or 18 7 per cent however when more information was obtained the number of false positives was reduced to 57 or 11 6 per cent The term *false positive* is given in quotes to indicate that it is false only insofar as we do not have further information about these patients

Study of the group of 57 false positives gives the following information The average age of the patients was 65 0 years In 2 cases postmortem examination of the heart was negative in one of these the autopsy was not witnessed by any of the authors In 6 patients in whom the ECG was entirely normal 1 (age 39) had chest pain but no previous ECGs another (age 71) had myocardial infarction suspected clinically another (age 41) had cardiac neurosis another (age 75) had a Stokes Adams attack and the last two (ages 60 and 77) had no previous ECGs to render the BestΔ different from the ECGΔ Of the remaining 49 patients 6 had a history of myocardial infarction or myocardial infarction was suspected clinically besides these 14 had angina and 3 had less well defined chest pain There were 20 cases of left ventricular hypertrophy 3 cases of right ventricular hypertrophy or enlargement and 6 cases of right bundle branch block Although right bundle branch block does not generally interfere with the diagnosis of myocardial infarction in some cases it rendered it less certain Eleven patients had no

Table III Result of combining + and − diagnoses for myocardial infarction in PCG Δ ECG Δ and Best Δ out of 493 cases

PCG Δ agreement (as to occurrence or nonoccurrence of infarction)	With ECG Δ (cases)	With Best Δ (cases)
Complete as to location of infarction	93	162
Not complete as to location	53	53
As to occurrence of infarction	146	215
As to nonoccurrence of infarction	173	174
Total agreement	319 (64 7%)	389 (78 9%)

Table IV False negatives and false positives in PCGΔ vs ECGΔ and BestΔ in 493 cases

	Based on ECG Δ (cases)	Based on Best Δ (cases)
PCG false negatives	3 (0 6%)	10 (2 0%)
PCG false positives	92 (18 7%)	57 (11 6%)

All [illegible]

previous ECGs so that the BestΔ and the ECGΔ were identical

In the group of 493 cases the diagnosis of infarction both transmural and subendocardial was made in 227 cases In these 227 cases the diagnosis of infarction based on the standard 12 lead ECG alone was made in 150 cases or 66 1 per cent In the same 227 cases the diagnosis of infarction based on the PCG taken at the same time as the ECG was made in 215 cases or 94 7 per cent

Discussion

The ECG is most reliable in the diagnosis of recent infarction Old infarctions often present considerable difficulty and in some cases the ECG can return to normal [9] The present work demonstrates that the single PCG can provide a diagnosis of infarction in a substantial number of cases in which the diagnosis of previous infarction could not be made on the basis of the single ECG It appears therefore that the PCG may be of considerable value in the diagnosis of coronary heart disease

The diagnosis of myocardial infarction can be made on the basis of the five simple criteria given in nearly every case in which such a diagnosis may be arrived at from the electrocardiogram The only exceptions to this appear to be a few cases of subendocardial infarction and one case of transmural infarction in which the PCGΔ was doubtful Since the polarcardiographic criteria relate only to the QRS complex and since the electrocardiographic diagnosis of subendocardial infarction relates to the S T segment and the T wave it might have been expected that the diagnosis of subendocardial infarction would be missed in all cases However the restriction of diagnostic criteria to the QRS complex is no more necessary for the PCG than for the ECG The fact that only 3 of the 21 cases of subendocardial infarction diagnosed from the ECG did not show QRS abnormalities visible in the PCG suggests that the distinction usually drawn between subendocardial and transmural infarction may be less than that commonly supposed

The small number of false negatives is an expression of the fact that when the diagnosis of myocardial infarction can be made from a single electrocardiogram it can also be made on the basis of the five polarcardiographic criteria If the number of false positives were also small it would indicate that the Polarcardiograph was very nearly equivalent to the electrocardiograph as a diagnostic tool and despite the simplicity of the polarcardiographic diagnostic criteria there would probably not be sufficient grounds for adopting the Polarcardiograph clinically As it turns out however there are significantly more false positives and this suggests that the Polarcardiograph provides a display which is more sensitive to the electrical abnormalities resulting from infarction When more information is obtained the number of false positives becomes less Expressed another way there is a tendency for the BestΔ and the PCGΔ to converge

It will be recognized that the diagnostic criteria should manifest themselves in the corresponding VCG loops Defining a clockwise rotation with respect to the origin as one in which longitudes become less negative or more positive we find that downslopes in the β_{QRS} and γ_{QRS} tracings appear as clockwise rotations in the corresponding segments of the VCG loops in the transverse and left sagittal planes respectively The return of the transverse magnitude to the origin following an initial deflection is clearly shown in the reconstructed loop in Fig 2D It might be expected from these relationships that the vectorcardiogram would be just as useful as the polarcardiogram in the application of the criteria mentioned This in practice is not the case because the origin of VCG loops is not defined with sufficient accuracy This limitation of accuracy is due only in part to the burnt out appearance at the origin In the VCG display the location of the origin is determined from a single beat The ECG on the other hand because of its expansion on a time scale permits the determination of a base line from the study of a series of beats However the VCG responds to components of the heart vector in two directions whereas a single ECG lead responds to components in only one direction The spatial magnitude tracing of the PCG responds to components in three directions and its expan

sion on a time scale permits comparison of several beats The base line is set automatically after each heartbeat (Fig 2B) When the base line is correctly set all deflections of the spatial magnitude tracing should be upward Downward deflections are quite obvious and immediately reveal an incorrect base line setting It is the accuracy of the base line determination provided by the Polarcardiograph that permits the recognition of abnormalities in initial QRS vectors necessary for the criteria employed in this study

Summary

The usefulness of five simple criteria for the polarcardiographic diagnosis of myocardial infarction was evaluated in 493 patients of whom 227 were considered on the basis of ECG or postmortem evidence to have suffered infarction In these the criteria gave the diagnosis in 94 7 per cent On the other hand two independent readers using conventional criteria reached the diagnosis from the single ECG recorded at the same time as the PCG in only 66 1 per cent In 11 6 per cent of the total population the criteria indicated myocardial infarctions which could not be confirmed by available evidence The results indicate that the Polarcardiograph may be of considerable value in the diagnosis of coronary heart disease

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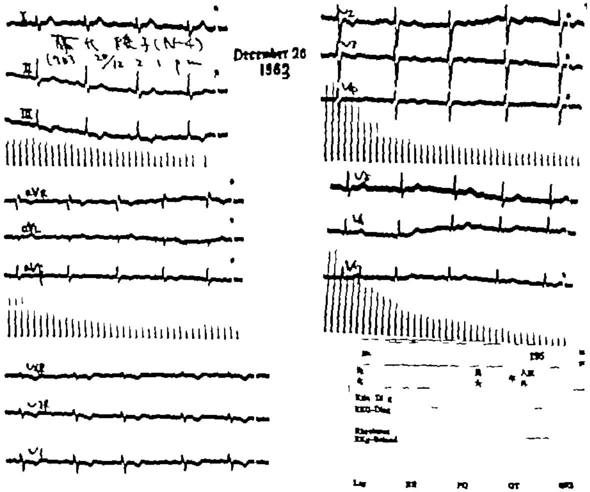


Fig. 2. Electrocardiogram showing sinus rhythm, QRS axis of +90 degrees, normal T wave, P-Q interval of 0.14 sec., R/S ratio in Lead V[illegible] of 0.7/0.9 mV. and in Lead V[illegible] of 1.5/0.7 mV., intrinsicoid deflection of 0.3 sec., and ST-T segment within normal limits.

the time of the angiocardiography failed to demonstrate any evidence of shunting or pressure gradient across the pulmonary valve and the tricuspid valve (Table I).

Diagnosis. On the basis of the facts obtained the following possibilities were considered: (1) Because of the heart sounds, either an atrial septal defect with increased flow or a pulmonary stenosis seemed to be possible, but both were ruled out by catheterization studies. The intensity of the murmur as well as the recent discovery of it were very significant. If the components of the second pulmonary sound were interpreted as splitting of the second sound, the rest of the findings were somewhat paradoxical and would constitute a rather uncommon situation, since in spite of an almost normal function of the pulmonary valve there was no question as to the disturbance in right ventricular ejection. (2) Because of the angiocardiographic findings, consideration of a solid mass might have been a rather positive approach. The recent appearance of the intraventricular mass might have indicated a thrombus or cardiac tumor. However, there were no symptoms or signs in the past that would support the possibility of a thrombus. Among the primary tumors of the heart, likely possibilities

Table I. Cardiac catheterization data

Site	Pressure (mm. Hg) Systolic/diastolic	O_2 saturation (%)
Superior vena cava	9/4	69
Inferior vena cava	8/5	72
Right atrium	7/3	[illegible]0
Right ventricle	44	7[illegible]
Main pulmonary artery	3[illegible]/[illegible]	[illegible]0
Wedged pulmonary artery	18/10	—
Femoral artery	100/60	95

in order of frequency, were myxoma, sarcoma, and rhabdomyoma. The good hemodynamic status as well as clinical condition would probably rule out the sarcoma, and the absence of symptoms or signs in the central nervous system, the absence of intracardiac conduction disturbances, and the appearance of the defect across the pulmonary valve would also rule out the rhabdomyoma. Among the myxomas of the right heart, their higher frequency in the right atrium is a well-known fact, but this was not the case, and the site of origin would have been at the right ventricular level, since the function of the tricuspid valve was not impaired. In spite of the difficulties in establishing a diagnosis of right intraventricular myxoma, it was the best possibility as a preoperative diagnosis.

Operative findings. Surgical exploration was performed under mild general hypothermia and extracorporeal circulation on Jan. 24, 1964. The heart was approached through a median sternotomy, and no abnormalities were found at the pericardium, the right atrium, and the right ventricle externally. A thrill was palpable over the outflow tract of the right ventricle and across the pulmonary valve toward the root of the pulmonary trunk. The systolic beat of a semisolid mass-like structure was felt inconstantly by digital palpation just above the pulmonary ring; however, external palpation of the right ventricle identified no mass. After installation of the extracorporeal circuit, a right longitudinal ventriculotomy about 6 cm. long was made at the outflow tract, the ventricular wall being about 0.5 cm. thick. When the ventricle was opened, a tumor which consisted partially of a mass resembling a blood clot and which was partially gelatinous

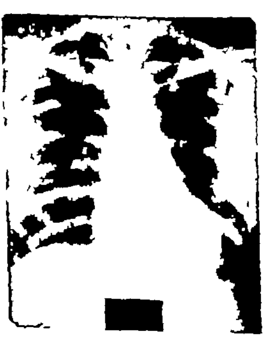


Fig. 3. Chest x-ray film showing normal-sized cardiac silhouette and normal pulmonary fields.



Fig. 4. Selective angiocardiogram showing the filling defect at the right ventricular outflow tract as indicated by the arrows.

and myxomatous was visualized. Part of the tumor had prolapsed into the pulmonary artery and was even being held by the peri-arterial tape; when released, it entered the ventricular cavity. The mass was found to arise from the most anterior part of the crista supraventricularis and adhered loosely to the chordae tendineae of the anterior leaflet of the tricuspid valve. The tumor was resected by scissor dissection at those sites (Figs. 6 and 7). The right atrium, the remainder of the right ventricle, and the trunk of the pulmonary artery were found by inspection and palpation to be normal. The heart-lung bypass lasted 23 minutes, and recovery of the cardiac function was uneventful. Postoperatively, the heart murmur disappeared completely, and the patient was discharged 17 days after the operation.

The tumor weighed 30 grams. Microscopically, the findings were compatible with those described in cases of myxoma (Figs. 8 and 9).

Discussion

Intracardiac primary tumors are rare. In our Institute, 3,832 cardiac operations were performed from 1951 to late February, 1964, and only 4 cases of primary tumors, including the present one, have been found. Among these, there was one rhabdomyoma[16] and 2 left atrial myxomas.

As for the etiology of these intracardiac myxomas,[4,7] it has been postulated that



Fig 9 Microscopic aspect of the myxoma showing the stroma formed by mucin scattered spindle shaped cells stellate cells and a few big multinucleated cells

2 CARDIAC MURMUR A murmur resembling that in pulmonary stenosis is heard over the pulmonary valve area Changes in the intensity of the murmur from one day to another have been reported [11] but there seems to be no influence of the body position such as has been observed in the case of atrial myxomas The phonocardiogram of the present case showed an ejection murmur and an abnormal sound that was best recorded at the pulmonary valve area Although it might be considered to be a split second sound the temporal relationship is beyond the usual time recognized as splitting Furthermore the recent discovery of the murmur and the absence of fever is a feature to be taken into consideration

3 STANDARD CHEST X-RAY FILM The x-ray film is usually normal[13] or might show right ventricular enlargement dilated pulmonary conus shadow or increased clarity of the pulmonary fields [10,11]

4 ELECTROCARDIOGRAM Right axis deviation [10] right ventricular hypertrophy [11,14] right bundle branch block [11] and inverted T waves in the precordial leads[10,13] have been described The tracing recorded in our case was within normal limits

5 CARDIAC CATHETERIZATION All the cases in which catheterization studies were made but ours showed a systolic pressure gradient across the pulmonary valve Gottsegen and associates[14] emphasized the multiple changes in the pressure tracing perhaps related to the positional changes of the tumor by manipulation However such changes are by no means specific and should not be relied upon with great expectations [11,14]

6 ANGIOCARDIOGRAPHY Intracavitary tumors may produce peculiar filling defects [13,14] and the size as well as the form and location of the mass can be evaluated with accuracy by means of angiocardiography [3]

Diagnosis Suggestive diagnostic features are (1) the presence of a cardiac murmur closely resembling that heard in pulmonary stenosis (2) the presence of right ventricular enlargement dilatation of the pulmonary artery and increased clarity of the pulmonary fields on the chest x-ray film (3) the finding of right ventricular hypertrophy or right bundle branch block on the electrocardiogram (4) the presence of a systolic pressure gradient across the pulmonary valve without evidence of left to right shunt by cardiac catheterization studies (5) the demonstration of a filling defect which by angiocardiography is unequivocal

Diagnostic features 1 through 4 are completely similar to those found in pulmonary stenosis and minimal doubt as to the diagnosis of pulmonary stenosis should make us suspect the possibility of a tumor so that adequate studies can be performed Gottsegen and associates[14] emphasize the following features to enable us to make a correct clinical diagnosis (1) syncopal attack which is rare as a manifestation of pulmonary stenosis alone (2) hemodynamic changes difficult to explain on the basis of the features of well known common entities (3) a sudden onset a rapidly worsening and a medically intractable clinical course Kishimoto's patient[10] suc

cumbed after 3 months of clinical evolution and the patient reported on by MacRae and Galea[13] died just a few weeks after initiation of the symptoms. Gottsegen's patient[14] showed a rather rapid deterioration while different diagnostic procedures were being done.

The characteristics of the systolic thrill which were described as "feeling like a worm moving upward from the third to the second intercostal space" have been found rather frequently in our Institute in cases of aneurysm of the sinus of Valsalva and the present case was initially thought to be that of such an entity compressing the outflow tract of the right ventricle and was worked up accordingly.

To summarize, if any doubt exists angiocardiographic studies should be performed.

Differential diagnosis. The following entities should be born in mind as necessary diagnostic steps: (1) pulmonary stenosis (valvular and infundibular type), (2) aneurysm from the left heart sticking into the right ventricle, nonperforated aneurysm of the sinus of Valsalva,[4] aneurysms of the membranous portion of the interventricular septum, etc., (3) right atrial myxoma, especially one that has prolapsed into the right ventricle, (4) other cardiac tumors and pseudotumors frequently found in the right ventricle, such as sarcoma,[15, 3] rhabdomyoma,[16] organized thrombus,[17] etc.

The nature of the mass cannot be determined by angiocardiography in spite of its unquestionable value as a diagnostic means. The endomyocardial biopsy technique[18] developed in our Institute and used for the diagnosis of fibroelastosis and cardiomyopathies in general might have been of great value in regard to this point.

Surgical considerations. Crafoord[1] in 1954 succeeded for the first time in the removal of a myxoma of the left atrium, and the constant improvement in and decreased risk from the techniques of extracorporeal circulation afford a more satisfactory approach to the treatment of these tumors so that, consequently, the number of cases successfully treated will increase.

Because of the friability of these myxomas, the likelihood of transoperative loss of blood, and the variable degree of myocardial damage secondary to the altered hemodynamics, removal under extracorporeal circulation is the safest procedure.[11, 6, 4] Pulmonary embolism should be avoided in cases of right ventricular myxomas just as systemic embolism must be avoided in cases of myxomas of the left heart.[11] Michaud[11] emphasizes a few points concerning the removal of right ventricular myxomas: (1) Hypothermia alone imposes a temporal restriction so that extracorporeal circulation must be used. (2) Bilateral thoracotomy with transverse sternotomy seems to be a better approach than the median sternotomy. (3) Care must be taken to provide adequate methods of filtering the blood that passes through the heart-lung machine in order to avoid embolism of tumor particles into the systemic circulation. (4) The pulmonary artery should always be clamped or taped and the right ventricular cavity should be thoroughly cleansed so as to remove all small particles of tumor.

Multifocality of sites of origin has been reported by Kishimoto and Sakaibori,[1] and it is said that myxomas of the right heart usually originate from the atrial septum so that, in addition to the ventricular cavity, the interatrial septum and the main pulmonary artery as well must be carefully examined. The taping of the main pulmonary artery must be performed only after careful determination of the location of the tip of the myxoma, since accidental transection of the tumor with subsequent pulmonary embolism is always a menace, and the tape must be placed distal to the prolapsing mass. The technical aspects of removing the myxoma itself are usually no problem, but because of the friability of these tumors, care must be taken not to break or crush them within the cardiac cavity.

Summary

Myxomas of the right ventricle are extremely rare. We have reported the case of an 18-year-old woman who had such a tumor that was correctly diagnosed preoperatively and was successfully treated by surgical removal. To our knowledge this constitutes the second case in the literature with such an outcome.

The clinical features of these myxomas

are ill defined but resemble those of pulmonary stenosis. The possibility of such a lesion should always be borne in mind and thought of whenever doubt arises while one is considering pulmonary stenosis as a work up diagnosis and angiocardiography should be performed in order to clarify this obscure point.

Intracardiac myxomas are histologically benign but hemodynamically malignant and the almost sure fatality from the embolic phenomenon urges us to diagnose it and treat it early enough.

A thorough review of the literature has been presented.

Addendum

After this paper had been submitted for publication 2 cases of right ventricular myxoma with successful removal were described one by Doohen and associates[44] and the other by Wada and associates.[45]

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Progressive injury current with metastatic tumor of the heart

Case report and review of the literature

Thomas R Harris M D
G Daniel Copeland M D
Daniel A Brody M D *
Memphis Tenn

Metastatic tumors which involve heart and pericardium are not unusual and have been reported to occur in as many as 21 per cent of the patients who die of malignant disease[1-10] The antemortem diagnosis of cardiac metastatic disease is less frequently made because clinical manifestations may not be marked or may be attributed to the underlying disease The presence of cardiac arrhythmias is one of the most frequently noticed abnormalities and when arrhythmias occur simultaneously with heart failure and pericardial effusion in a patient with known malignancy cardiac involvement is suggested

Electrocardiographic changes due to tumors of the heart may vary from mild nonspecific abnormalities[7] to serious arrhythmias and to marked alterations in morphology[11-17] In addition to arrhythmias and conduction defects changes suggestive of pericarditis[17,18] and of both atrial[19] and ventricular infarctions[8,20] have been reported In general the electrocardiogram *has not been particularly helpful in* the diagnosis of myocardial infiltration with tumor but electrocardiographic changes may occasionally support the clinical diagnosis and may rarely provide the clue leading to the correct antemortem diagnosis

Marked S T segment displacement (progressive and prolonged elevation) is an infrequent electrocardiographic finding with metastatic cardiac tumors Progressive electrocardiographic changes resembling myocardial injury in the following case suggested the correct diagnosis of a chest lesion prior to other evidence of the correct etiology

Case report

M J R a 64 year-old Negro woman was admitted for the second time to the West Tennessee Tuberculosis Hospital on Oct 23 1967 with complaints of cough loss in weight and a respiratory infection which had persisted for 2 months She had been in good health until 2 months prior to admission when she developed exertional dyspnea and a cough productive of thick white sputum There had been no hemoptysis anorexia orthopnea paroxysmal nocturnal dyspnea edema or chest pain There had been a 30 pound loss in weight although her appetite remained normal When cough and dyspnea persisted the patient reported to the health department for a chest x ray examination A cavitary lesion adjacent to the left hilar region was found (Fig 1) and she was subsequently admitted for further evaluation and treatment

The patient s past medical history included four previous hospital admissions She had developed a

From the Section of Cardiology Univ[illegible]ity of T[illegible] Memphis Tenn
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Address Department of Medicine [illegible]ty of T[illegible] [illegible] Ave Memphis T[illegible] 38103

perirectal abscess 10 years previously which in spite of treatment resulted in multiple perianal fistulae. These were treated surgically in 1953, 1958, and 1959 (first, second, and third admissions). She was then hospitalized at the West Tennessee Tuberculosis Hospital for 1 year which ended April 1960 (fourth admission). The diagnosis at this time was extrapulmonary tuberculosis with multiple tuberculous fistulous tracts and abscesses of the perirectal area. The perirectal abscess did not recur and she remained free of symptoms until onset of the present illness. Review of systems was otherwise noncontributory.

Physical examination revealed an alert, intelligent, cooperative woman who was lying comfortably in bed. She was afebrile with a blood pressure of 100/70 mm. Hg, regular pulse of 88 per minute, and a respiratory rate of 20 per minute. There was no abnormality of the head or mouth except for edentulism. The thyroid gland was normal, the neck veins were flat, and the carotid pulses were normal. The lungs were clear of rales, wheezes, or other abnormal sounds. The heart was normal in size and a soft, faint systolic murmur was heard at the apex and the lower left sternal border. The second heart sound was slightly accentuated at the heart base. Examination of the abdomen, pelvis, and rectum revealed no abnormality. There was no edema, clubbing, cyanosis, or deformity of the extremities; peripheral pulses were normal.

Significant laboratory studies included hematocrit 35 per cent, hemoglobin 12.3 Gm. per 100 ml., sedimentation rate 41 mm. per hour, leukocyte 8,250 per cubic millimeter with 78 per cent segmented and 2 per cent nonsegmented neutrophil, 14 per cent lymphocytes, and 6 per cent monocytes. Serum electrolytes, sickle-cell preparation, SGOT, and urinalyses were all normal. Histoplasmin skin test and fungus serology for histoplasmosis, blastomycosis, and coccidioidomycosis were negative. The wheal which resulted from the intermediate PPD skin test measured 10 mm. in 48 hours. Five examinations of sputum were negative for acid-fast bacilli. One of five cytological examinations of sputum revealed atypical cells.

X-ray examination. Posteroanterior and right lateral chest films revealed a well-circumscribed infiltrate with cavitation located in the superior segment of the lower lobe of the left lung adjacent to the cardiac shadow. A review of previous films in retrospect suggested the presence of a nodular lesion in this area during the previous hospitalization 18 months earlier.

Electrocardiography. The admission electrocardiogram (Fig. 2) of October 23 was abnormal. There was a sinus rhythm of 100 per minute. The mean QRS axis was +35 degrees in the frontal plane and the mean T axis was 110 degrees. A small Q was present in Leads I and aV~L~. Definite S-T segment elevation occurred in Leads aV~L~, I, and V~2~-V~6~, and the T waves were inverted in those leads. Initially these changes were thought to suggest an acute anterolateral myocardial infarction.

All tracings [illegible] Cambridge electrocardiograph and calibrated [illegible] of [illegible] unchanged.

Clinical course. During her hospitalization the patient had low-grade fever and even though her sputum was negative the initial diagnosis was pulmonary tuberculosis. Therefore she was treated with isoniazid and para-aminosalicylic acid. Because of her abnormal electrocardiogram, serial studies of SGOT and LDH were obtained but no elevation of these enzymes occurred. During the next 6 weeks, repeated electrocardiograms, chest x-ray films, and studies of sputum were made and supraclavicular node biopsy was done. Chest films, bronchoscopy, and supraclavicular node biopsy were not diagnostic. The electrocardiograms revealed persistence indeed progression of the marked S-T segment elevation. At this time the working diagnosis was metastatic carcinoma to the heart from a primary site in the lung. Since other studies were not diagnostic, the progressive electrocardiographic changes were thought to give considerable weight to this diagnosis. A pericardial friction rub was present for a few days in January, 1963. At no time was the patient aware of cardiac difficulty and she had no chest pain. Repeat bronchoscopy on Jan. 28, 1963, demonstrated a lesion in the left bronchial tree which on biopsy proved to be typical squamous-cell bronchogenic carcinoma. The patient developed gastrointestinal difficulty, her general condition deteriorated, and she died on Feb. 14, 1963, after a hospital stay of 114 days.

Postmortem examination. Details of this examination will be limited to the cardiac pathology. The heart (Fig. 3) weighed 310 grams. Pericardial fat was increased and thickened pericardium was focally attached to myocardium. Irregular, firm, white metastatic tumor nodules which measured as much as 2 cm. in diameter were scattered over the pericardium. There was superficial tumor infiltration of the adventitial layer of the aorta at the level of the tracheal bifurcation and there was a flattened laminated mural thrombus (3 by 2 by 2.5 cm. in size) located on the inferior border of the aortic arch. The left ventricle was markedly infiltrated on its anteroseptal and lateral walls with firm white tumor nodules. In one area they protruded into the endocardial cavity and the papillary muscles of the left ventricle contained tumor infiltration. Section of the right ventricle revealed a large irregular firm intramural tumor measuring 3 by 3 by 1.5 cm. within the posterolateral wall. The endocardium corresponding to this area was covered by a flattened mural thrombus. An organized laminated pulmonary embolus with widely open lumen was also found in the left pulmonary artery. The coronary arteries contained a few focal atheromatous plaques but all lumens were open.

Microscopic sections of myocardium (Fig. 4) revealed extensive areas involved by neoplasm. Large tumor cell masses were located on the epicardial surface with prominent infiltration into the myocardium; at times the infiltration extended through the entire thickness of the myocardium. The tumor was characterized by nests of large eosinophilic cells with prominent nuclei which resembled squamous epithelial cells. Many epithelial and keratin pearls were evident. Large areas of necrosis with loss of cell morphology and cystic degeneration were prominent within the tumor

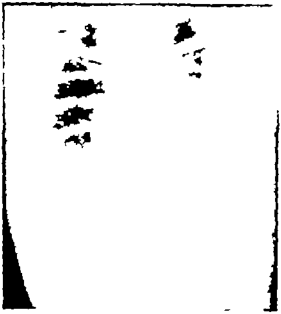


Fig. 1. Chest x-[illegible] showing [illegible] pulmonary lesion adjacent to the cardiac shadow.

metastases. The liver [illegible] necrosis with tumor [illegible] seen in all areas sectioned. Myocardial [illegible] by tumor was not unusual [illegible] appearance [illegible] minimum degree of [illegible] inflammatory reaction was present over the epithelial surface adjacent to tumor implant.

[illegible] The postmortem examination confirmed the clinical diagnosis of bronchogenic carcinoma of the left lung with extensive metastases. In addition to involvement of the heart and pericardium, there were metastases to peritracheal nodes, [illegible] external layer of the aorta, pancreas, right kidney, duodenum, and ileum. A duodenal mass previously demonstrated on x-ray examination proved to be metastatic polypoid tumor in the second portion of the duodenum. A similar lesion in the proximal ileum was at the leading margin of an ileoileal intussusception which was a major contributing factor to the patient's death.

Discussion

The marked degree of S-T segment elevation demonstrated in this patient's electrocardiograms for a period of 4 months is most unusual. The progressive increase in this injury current associated with development of a pathologic Q and other electrocardiographic changes resembling those of myocardial infarction is a unique finding in neoplastic infiltration of the heart. The absence of primary or secondary myocardial disease other than neoplastic infiltration suggests that the persistent monophasic wave and progressive S-T segment displacement are related to this involvement. The present report is the second instance in which marked S-T displacement is recorded in metastatic tumor of the heart[7] and the third instance found in which there is persistence of a monophasic wave for months.

Pronounced and persistent S-T segment displacement in a case of metastatic tumor of the heart was first reported by Rosenbaum[1] in 1944. Marked elevation of the S-T segment occurred and persisted for the remaining $2\frac{1}{2}$ months of the patient's life. Marked S-T displacement for prolonged periods of time is rare, and in addition to the above mentioned case that of a child in whom S-T displacement was present for several months is discussed by Sodi Pallares. In the latter case the findings of chronic inflammatory areas of syphilitic myocarditis as well as healed myocardial infarction are offered as an explanation of the marked displacement over so long a period of time. Barnes[8] believed that elevation of the level of the take-off of the RS-T segment would not be anticipated from tumorous invasion of the left ventricle, for the acute cellular and vascular reaction which follows acute myocardial infarction is lacking. However, in Rosenbaum's case the authors believed that the long duration of the S-T displacement could be attributed to repeated injuries or to sustained injuries which prevented the formation of new cell membrane or that it might be due to continuous neoplastic infiltration of uninvolved muscle. It has been postulated that S-T segment deviation is related to changes in potassium and sodium gradients across the myocardial cell membrane[4]; hence, it would seem to be reasonable that continuous neoplastic infiltration of myocardium could result in damage to the myocardial cell membrane with a loss of intracellular potassium and an increase in intracellular sodium. These changes could produce an altered transmembrane ionic gradient which would be indicated in the electrocardiogram by S-T segment elevation. The marked myocardial infiltration by tumor in the present case would, in the absence of other explanation, seem to support this possibility.

The prominent association of necrosis

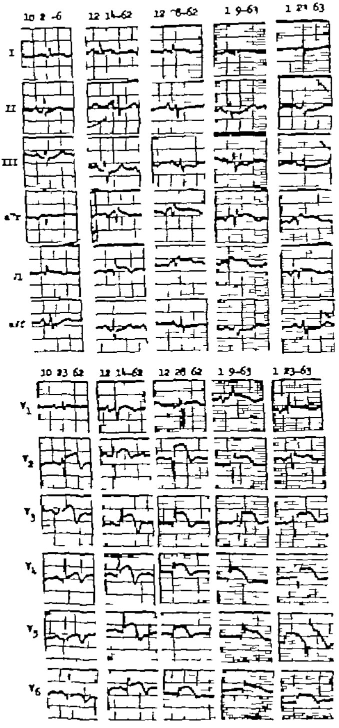


Fig. Serial electrocardiograms demonstrating the progressive changes. Electrocardiograms show significant S-T segment elevation beginning with the initial tracing. There is progression and persistence of this elevation over the following month. In addition to marked S-T segment elevation and T wave inversion seen in the earliest tracings, reciprocal S-T segment depression in Leads III and V_F and definitely abnormal Q waves appear in the later tracings. The appearance of a conduction defect is demonstrated by the appearance of rsR in Lead V_1 in the tracing of 1-9-63.



Fig 3 The heart Extensive myocardial infiltration by tumor is apparent

with tumor infiltration in the present case may be the clue to the explanation of the unusual electrocardiographic changes The role of necrosis in the origin of electrocardiographic changes characteristic of myocardial infarction has been studied in recent investigations [3, 4] It has been shown that the appearance of monophasic waves occurs when necrotic tissue is placed in contact with unaffected myocardium By this method it has been possible to reproduce all the electrocardiographic changes of myocardial infarction including typical QRS S T and T wave changes The cause of this phenomenon has been shown to be related to the ionic transfer of potassium since application of necrotic tissue or potassium chloride solution to the myocardium has a similar effect Additional experiments have shown that the myocardium is affected and electrocardiographic changes produced only if the necrotic tissue contains potassium It has been demonstrated that potassium ions are really transferred from necrotic tissue to healthy myocardium and that the potassium after leaving injured cells has a depolarizing effect on surrounding myocardium When one considers these observations the transfer of potassium ions from the necrotic areas of tumor infiltration into contiguous myocardium seems to be a logical explanation for the changes observed in the present case The long duration and the progression of the electrocardiographic changes would then be explained by additional necrosis as the tumor continued its growth

Electrocardiographic findings in a proved case of tumor of the heart was first published by Lloyd[17] in 1929 In 1933 Siegel and Young [5] summarized the electrocardiographic findings in the previous cases and reported the fourth case of metastatic tumor of the heart with published electrocardiograms The S T segment changes in the four illustrated electrocardiograms show little variation in serial tracings over a period of 16 days and deviation from the isoelectric line is minimal In a case of primary sarcoma of the pericardium with moderate myocardial invasion published by Bowman[22] in 1938 the electrocardiograms showed S T and T wave changes which were thought to simulate closely those obtained in cases of recent coronary thrombosis Reuling [23] in 1941 reported a case in which the clinical diagnosis of metastatic carcinoma of the heart was made by progressive electrocardiographic changes and stated that only 8 previous

cases of secondary tumors of the heart had been diagnosed during life. His case was marked by several arrhythmias but examination of the published electrocardiograms shows no particularly significant S-T changes. Bisel and associates[7] in 1953 summarized electrocardiographic findings in 59 patients with cardiac metastases and in only 3 was S-T segment deviation mentioned. Forty-two per cent of their patients had a normal electrocardiogram and in only 28.8 per cent of the cases was



Fig. 4. Photomicrographs of heart. *Above,* Myocardium is extensively infiltrated with tumor. Hematoxylin and eosin stain ×100. *Below,* Tumor infiltration and marked necrosis completely obscure normal myocardial architecture. Hematoxylin and eosin ×100.

an abnormal electrocardiogram thought to be due probably to cardiac metastases In 1955 Goldman[8] described 217 cases of metastatic tumor to the heart or pericardium in 57 of which there were electrocardiograms In 3 of these cases there were progressive ECG changes which were due in one instance each to diffuse nodular metastases to right heart metastases and to other heart disease In describing major electrocardiographic changes in 27 patients with significant metastatic lesions in the pericardium Thurber[7] mentions S T segment depression in 6 but makes no statement about S T elevation Twenty five of the 27 patients had some T wave abnormality

S T segment displacements and T wave abnormalities may be seen in normal persons and in those with pericarditis myocarditis myocardial ischemia myocardial infarction and myocardial aneurysm In addition temporary S T segment deviations may be seen in a wide variety of nonischemic clinical conditions in which they are reversible by appropriate therapy [4] Displacement of the S T segment and T wave abnormalities are characteristic electrocardiographic findings in pericarditis The S T segment displacement is ascribed to the underlying myocarditis and accounts for the current of injury which is seen in acute pericarditis Abnormal repolarization is manifested by the abnormalities in the T wave and may persist for years but the S T segment displacement is seen only with active pericarditis

In the absence of typical QRS changes of myocardial infarction the differentiation between pericarditis (or perimyocarditis) and injury due to ischemic heart disease is a frequent clinical problem According to Schwab and Herrmann[5] the following changes suggest ischemic origin rather than pericarditis (1) S T displacement more than 4 or 5 mm (2) deep T wave inversion (3) monophasic wave due to fusion of the S T segment and the T wave (4) Pardee T wave (5) reciprocal S T segment displacement in the standard limb leads Exceptions to the first two are encountered occasionally in pericarditis but exceptions to the last three are rare [25]

It is now generally recognized that persistence of positive displacement of S T segments is frequently found with cardiac aneurysms This elevation has been found to be present in 75 to 90 per cent of the cases of ventricular aneurysm [24] Goldberger[24] thought that the electrocardiographic pattern is characteristic in ventricular aneurysms and that an upward QRS complex in Lead aV_R is both necessary for and pathognomonic of the diagnosis of ventricular aneurysm but absence of the upward QRS complex in Lead aV_R has been reported in a case of posterior wall aneurysm [27] Persistence of the electrocardiographic pattern of acute myocardial infarction for several months is very suggestive of ventricular aneurysm In these instances the initial electrocardiographic pattern of acute infarction is present but after the acute changes have subsided the displaced S T segment remains elevated Progressive elevations of the displaced segment are not reported with ventricular aneurysm In hearts with chronic diffuse myocardial damage persistent elevation of the S T segment has been found in patients with infarction but without associated aneurysm [28] The explanation of the S T displacement in the case of cardiac aneurysm appears to be more difficult than the explanation of those S T displacements associated with myocarditis or myocardial ischemia In the latter instances myocardial inflammation or anoxia could cause cellular damage with loss of potassium ions to nearby myocardial tissue In the case of cardiac aneurysm with persistence of S T segment displacement there is no inflammation and the injury is said to be due to mechanical trauma It has been suggested that there is a struggle between healing and microscopic occlusion of new small vessels At present a more exact explanation must await further study

Consideration of the usual clinical conditions associated with injury current and comparison with the clinical features and pathologic findings in the present case is of interest In most cases S T segment elevation can be explained by injury of various amounts of myocardial tissue The injury in the present case may be ascribed to extensive tumor infiltration of the myocardium The belief that S T segment deviations may be due to altered

membrane gradients resulting from shifts in potassium ion is supported by the prominent association of necrosis with the tumor infiltration. The progressive injury current demonstrated in this case of metastatic tumor is of interest because of its rarity and because of the association with necrosis and tumor infiltration.

Summary

The case of a patient with metastatic tumor of the heart who demonstrated progressive and prolonged S-T segment elevation with other electrocardiographic changes suggestive of myocardial infarction is reported. The infrequency of this finding in cases of tumors of the heart is mentioned and other clinical conditions in which S-T segment deviation occur are discussed. Attention is called to the association of necrosis with electrocardiographic changes characteristic of myocardial infarction.

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Review

Cardiac metabolism

The effect of some physiologic, pharmacologic, and pathologic influences

*Lionel H. Opie, M.D. (Cape Town), D. Phil. (Oxon.), M.R.C.P.**
Bellville, South Africa

A biochemical approach to cardiology is increasing in favor among research workers attempting to explain patterns of myocardial behavior in health and disease. Already available are a number of excellent and detailed articles which review cardiac metabolism,[1-3] but few appear to be written for practicing cardiologists who need the major trends in cardiac metabolism succinctly outlined as a background to their fuller understanding of various clinical problems. Such is the aim of this review.

The basics of cardiac metabolism

The myocardial metabolism of carbohydrate and fat is largely concerned with the uptake and oxidation or storage of these fuels and the concomitant process of high-energy bond generation in the form of adenosine triphosphate (ATP). The protein metabolism is more intimately concerned with the complex interaction between actin, myosin, and ATP resulting in contraction. The pathways of metabolism of carbohydrate and fat are relatively simple and better understood; those of protein metabolism are complex but of primary importance to the elucidation of heart muscle metabolism.

The earliest studies of myocardial metabolism were those of Locke and Rosenheim[4] in 1907, who used the isolated perfused mammalian heart to establish the myocardial uptake of glucose. This power of consuming sugar was impaired by pancreatectomy.[5] In 1914, Evans[6] found that carbohydrate oxidation could supply only one third of the heart's energy. The source of the remainder of the energy was probably the direct combustion of fat.[7] Not until the introduction of coronary sinus catheterization by Bing[8] and his colleagues in 1947 could the importance of fatty acids as substrate for the human heart be proved.[9] More recently, isolated heart preparations have been used in combination with radioisotopic labeling of substrates to confirm the importance of fatty acids as a major myocardial fuel. Fatty acids not only provide energy through oxidation, but exert actual control over the intracellular fate of glucose.[10,11] In vivo, the myocardial uptake of fatty acid is probably related to the arterial level of free (= unesterified) fatty acids and triglycerides; therefore, the elevated level of fatty acids in the postprandial and fasting states are associated with predominant usage of fat by the heart. The rich stores of endogenous lipids can also act as substrate.[12]

Although fatty acids, glucose, and lactate are the major myocardial foods, the heart is omnivorous, and ketones, amino acids, and pyruvate can all be taken up in rough proportion to the arterial level.

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*Lecturer in Medicine, University of Stellenbosch Medical School; Physician, Karl Bremer Hospital, Bellville, South Africa. Present address: Department of Biochemistry, University of Oxford, Oxford, England.

The reactions that break down these substrates have one common result: the feeding of short carbon chains into the Krebs cycle where the major share of cellular oxidation occurs and the associated process of phosphorylation of ADP to ATP is achieved by enzymatic dehydrogenation and the passage of the released hydrogen along the respiratory chain before combining with oxygen to form water. The details of the processes coupling oxygen usage to the generation of ATP from ADP and inorganic phosphate are as yet obscure but the problem is receiving the closest scrutiny of modern biochemistry.

The major part of the energy produced is consumed in contraction because when the heart stops but coronary perfusion is maintained the uptake of oxygen falls to about 20 to 35 per cent of that of the beating level.[13] Furthermore, the uptake of oxygen by slices of rat ventricle and human atrium incubated with pyruvate is 30 to 40 per cent of the uptake of beating intact hearts.[14] It seems therefore that 60 to 80 per cent of myocardial energy metabolism is directed toward the contractile mechanisms.

Basic to contractility are the ill understood reactions between actin and myosin coinciding with electrical systole and resulting in muscular contraction. The two proteins actin and myosin can be combined into threads which contract when ATP is added.[15] Similarly, actomyosin bands prepared from human hearts contract in the presence of ATP.[16] Furthermore, myosin has ATPase activity. The role of ATP in muscular contraction has been questioned by the frequent failure to demonstrate the breakdown of ATP or even creatine phosphate during a single muscle twitch.[17] Recently, however, Davies[18] found ATP breakdown in proportion to the work done by the frog rectus abdominis. Furthermore, the weight of biologic evidence favors the dominant role of ATP in contraction, possibly as follows:[5]

$$\text{Myosin} + \text{actin} \rightarrow \text{actomyosin}$$

$$\text{ATP} + \text{actomyosin} \rightarrow \text{myosin} - \text{ATP} + \text{actin}$$

$$\text{Myosin} - \text{ATP} + H_2O \rightarrow \text{ADP} + P_i + \text{myosin}$$

The ADP thus formed is essential for the coupling of phosphorylation to electron transport and Krebs cycle oxidations, processes associated with ATP regeneration. Therefore the production and utilization of energy are intimately linked and interdependent.

Muscular contraction described in anatomic terms is also an interaction between actin and myosin. Actin interdigitates with myosin; during contraction it slides or folds between the myosin threads.[19]

Physiologic influences

A. Maintenance of cardiac force. Deprivation of substrates does not cause human heart failure, probably because of the wide range of potential exogenous and endogenous substrates. This does not apply to the isolated heart which becomes hypodynamic after 1 or 2 hours of activity when a suitable substrate is needed to restore the amplitude of contraction.[3] However, other substances not regarded as potential substrates can also be effective and these include egg yolk, bovine serum albumin, and a phospholipid called lysolecithin.[4, 5] The mechanism of this stimulatory action may be an increased myocardial uptake of calcium.[3] Spontaneous failure in the heart lung preparation in the presence of a normal extraction of substrates is related to diminished catecholamine and cholinergic content of the perfusing fluid.[27]

Hajdu and Leonard[4] described a system of plasma globulins, the cardioglobulins, which have an inotropic effect on frog heart. These globulins are increased in aortic stenosis and essential hypertension but decreased in congestive heart failure.

B. Heart rate. An arrhythmia per se does not alter the myocardial uptake of substrates and oxygen; hypoxic changes may, however, result from a rapid arrhythmia which curtails diastolic filling of the coronary arteries.[4]

C. Effect of pH. Isolated mammalian hearts deteriorate mechanically when the extracellular pH falls below 7.1 or 7.0 but in vivo a pH of 6.9 may be compatible with life. As the pH increases to 7.7, the uptake of glucose and the production of lactate increase, but the rates of oxidation of pyruvate and palmitate are only slightly altered over the range 7.1 to 7.7. There

fore pH affects glycolysis rather than the oxidative processes of the Krebs cycle.[28] Another effect of acidosis is decreased myocardial response to noradrenaline.

D. Effect of exercise. The increased demand for substrates during an acute work load in man is largely met by an increased coronary blood flow.[1] A severe load is associated with changes suggestive of hypoxia, namely an increased uptake of glucose, breakdown of glycogen and production of lactate, and decreased high energy bond formation and concentration.[29-31] Wollenberger[32] found a decreased myocardial labile phosphate content only when resistance but not flow work was increased.

During a prolonged work load there is an increased rate of protein synthesis,[33] which presumably corresponds to cardiac hypertrophy.

E. Effect of temperature. The decreased myocardial uptake of oxygen during hypothermia[7] is accompanied by greater longevity of the isolated mammalian heart[34] and by the conversion of a greater percentage of the glucose uptake into glycogen.[16] This protective effect of hypothermia is lost if ventricular fibrillation (with accompanying hypoxia) occurs.

F. Effect of hormones. Catecholamines and monoamine oxidase inhibitors are known to have a positive inotropic effect in many species including man.[37]

Conversely, reserpine reduces the myocardial content of noradrenaline and decreases the force of contraction.[38,39] The metabolic effects of catecholamines include an increased uptake of glucose, breakdown of glycogen, increased production of lactate and increased uptake of oxygen.[40] Both noradrenaline and adrenaline alter the metabolism as well as the dynamics of the heart.[8,41]

During catecholamine-induced glycogenolysis phosphorylase activation occurs under the stimulus of increased tissue levels of the co-enzyme 3',5'-cyclic adenosine monophosphate (AMP). Haugaard's[42] hypothesis is that ATP produced during glycogenolysis is degraded by systole to ADP, which regenerates AMP under the action of myokinase, thereby allowing the further promotion of glycogenolysis by catecholamines. However, the positive inotropic effect of catecholamines is not always related to the degree of glycogen depletion[43] or to the concentration of active phosphorylase,[44] nor is activation of phosphorylase necessary for the effect on smooth muscle.[45] The stimulatory action of catecholamines on glycogenolysis resembles the effect of an acute work load, and the above-mentioned metabolic effects may be secondary to the inotropic effects.

The inotropic effect of *corticosteroids* is demonstrated by (1) the action of glucocorticoids in restoring the force of cardiac contractility after adrenalectomy, (2) the reversal by cortisone of mechanical failure in the cat heart preparation, and (3) the direct positive inotropic effects of mineralocorticoids in isolated myocardium.[46,47] Glucocorticoids also impair the myocardial metabolism of glucose and pyruvate, by an unknown mechanism.[48]

The role of some other hormones has recently been outlined by Beznak and Tanz.[49] Both growth and thyroid hormones are needed for maximal cardiac hypertrophy to develop after aortic constriction in rats. Oxytocin increases cardiac rate and output, and has been found to reduce hypothermic fibrillation in dogs.[50] Estradiol stops electrically induced fibrillation in the isolated rat heart.[5]

Pharmacologic stimuli

A. Cardiac glycosides. The manifold ways in which cardiac glycosides may affect the myocardium include the following.

First, the transmembrane flux of electrolytes is altered. The entry of sodium and calcium and the egress of potassium are enhanced. Calcium is needed for at least two glycosidic actions: the stimulation of oxygen uptake by human heart slices[51] and the inotropic effect on actomyosin bands prepared from failing hearts.[5]

Secondly, the glycosides have an insulin-like effect in increasing the myocardial uptake of both glucose and nonmetabolized sugars such as galactose.

Evidence for a third possible action, on the generation of high-energy bonds, was fully reviewed by Wollenberger,[52] with the conclusion that the formation of ATP and creatine phosphate was probably not influenced.

Credit for the most modern hypothesis

goes to Olson[3] who suggests a catalytic action whereby the behavior of the contractile proteins is modified. Supporting this is the recovery of tritium-labeled digitoxin in the cytoplasmic fraction of ultracentrifuged heart muscle; this layer contains the contractile proteins. Further analysis has shown a binding of digitoxin to myosin in a molar ratio of one. An effect on the contractile proteins is compatible with the clinical observation that cardiac glycosides increase the mechanical efficiency but not the oxygen uptake of the failing human heart.[58]

B. Reserpine. Reserpine increases the sensitivity of both the normal and the thyrotoxic heart to digitalis.[illegible] This effect is apparently unrelated to the experimental finding that reserpine decreases *both the glucose uptake and the lipoprotein* lipase activity of heart muscle.[57,59]

C. Nicotine. The recent study by Oram and Sowton[61] establishes that nicotine causes dilatation rather than constriction of the coronary bed. Relative coronary insufficiency with angina pectoris results from increased cardiac work caused by elevation of blood pressure and/or tachycardia. Such effects are similar to those of sympathetic stimulation.

Pathologic conditions

In 1951 Olson and Schwartz[illegible] put forth a biochemical classification of heart failure. Disturbances in the production of energy such as those found in the high-output failure of anemia, thyrotoxicosis, and beriberi were contrasted with disturbances in the utilization of energy such as those that occurred in low-output congestive heart failure. Because there is not yet exactitude about the metabolic defects basic to the common types of heart failure, the classification used in the ensuing discussion is clinically rather than biochemically orientated.

A. Heredofamilial disease. The cardiac expressions of the muscular dystrophies may include tachycardia, arrhythmias, electrocardiographic changes, and even congestive failure. The abnormalities of the myocardial metabolism of carbohydrate found by Sundermeyer and associates[illegible] are not easy to interpret but do confirm *involvement of cardiac muscle.*

Heart disease is now described as a frequent complication of the Hurler and Marfan syndromes—diseases thought to be manifestations of inherited biochemical defects of connective tissue.[4]

B. Infective diseases. Fatty degeneration may occur in diphtheritic myocarditis. A similar lesion in the guinea pig is accompanied by impaired oxidation of fatty acids, the cause of which may be a decreased formation of the amino acid carnitine which is needed for the oxidation of fatty acids.[illegible]

C. Endocrine diseases. Patients with *thyrotoxicosis* have an increased coronary blood flow with an enhanced myocardial uptake of oxygen per beat.[illegible] The unaltered uptake of carbohydrate[illegible] implies therefore an increased consumption of oxygen *for an unchanged amount of substrate* burnt in the Krebs cycle, which is compatible with the uncoupling of phosphorylation from oxidation found in experimental hyperthyroidism.[illegible]

Thyroid hormones also have a specific effect on muscle. The rate of protein synthesis is decreased, creatine phosphate is broken down, and creatine phosphokinase is inhibited.[67]

The interdependence of thyroid hormones and catecholamines was shown by Brewster and associates,[illegible] who found that an intact sympathetic nervous system was required for the development of the hemodynamic changes of hyperthyroidism. Gaffney and associates[illegible] showed that the tachycardia induced by large doses of triiodothyronine was abolished by the simultaneous administration of a catechol amine antagonist, guanethidine. Thyroid hormone directly implanted into the heart can act as pacemaker in complete heart block—an action counterbalanced by reserpine.[70] Frye and Braunwald[illegible] describe an ingenious study in which increasing doses of triiodothyronine given to patients with atrial fibrillation correspondingly augmented the dose of digitalis required to control the ventricular rate. Patients treated with reserpine did not develop this type of resistance to digitalis.

These findings all argue for combined therapy with reserpine or guanethidine and digitalis in thyrotoxic heart failure.

Myxedema heart disease lacks a satis

factory explanation when one considers the decreased demand for oxygen of hypothyroid tissues and the clinical improvement in patients with intractable heart failure rendered hypothyroid. It is of much interest, therefore, that myxedematous patients with the apparent picture of heart failure do in fact have a normal response to the Valsalva maneuver[71]—a finding which argues strongly against myocardial failure, if this be accepted as that situation in which the heart is unable to respond to changes in filling pressure by appropriate changes in output.

D. Nutritional diseases

BERIBERI HEART FAILURE. The intimate association of this type of failure with thiamine deficiency is well established. Nevertheless, the exact metabolic lesion remains obscure.

Thiamine is involved in two glycolytic reactions and in one step in the Krebs cycle. First, there is the well-known role of thiamine pyrophosphate in pyruvate decarboxylation. Secondly, this thiamine derivative is concerned with the transketolase reaction of the pentose shunt, but the latter pathway is apparently of little importance in heart muscle. Because of the dominant importance of lipid metabolism in heart muscle, these defects in carbohydrate metabolism could not satisfactorily explain beriberi heart disease.

Impaired metabolism of pyruvate need not be associated with mechanical dysfunction of the heart, as shown by the normal myocardial contractility in uncontrolled diabetes mellitus in spite of decreased oxidation of pyruvate. Furthermore, no definite defect in myocardial function has been shown in volunteer human subjects or experimental animals with thiamine deficiency,[72] nor is there always an unequivocal deviation in the absolute uptake of pyruvate.[73] Furthermore, the total respiration of perfused hearts from thiamine-deficient rats is decreased without selective depression of pyruvate uptake, decarboxylation, or oxidation.[74]

A third reaction requiring thiamine pyrophosphate as cofactor is alpha ketoglutarate decarboxylation, a Krebs cycle reaction. In spite of a large accumulation of alpha ketoglutrate, experimental thiamine deficiency need not necessarily be accompanied by poor myocardial function.[7]

To explain such discrepancies, Huckabee[7] postulated a combination of thiamine deficiency with niacin or riboflavin deficiency, with one or both of the latter deficiencies causing abnormalities in the metabolism of nicotine adenine dinucleotide.

ALCOHOLIC CARDIOMYOPATHY. Alcoholism not only predisposes to beriberi heart failure but is associated with a specific cardiomyopathy.[75]

Apart from the finding that ethanol stimulates the myocardial uptake of oxygen,[76] there appears to be no data on the effect of ethanol on myocardial metabolism; therefore, the genesis of alcoholic cardiomyopathy remains unclarified. Because alcohol dehydrogenase is virtually absent from heart muscle, ethanol is unlikely to enter normal myocardial metabolic pathways and is thus unable to cause metabolic blocks by preferential usage. An alternative hypothesis is that ethanol may have a direct toxic effect on myocardial enzymes.

E. Idiopathic cardiomyopathy. This diagnosis is being applied with increasing frequency to a group of obscure diseases affecting the myocardium, endocardium, and even at times the pericardium. The Negroid peoples of tropical Africa, South Africa, and Jamaica are especially prone to idiopathic cardiomyopathy, but a somewhat similar disease occurs in other ethnic groups in a sporadic or familial distribution. Nutritional metabolic factors may possibly initiate or perpetuate some cardiomyopathies. For instance, the Ugandan disease may be linked to the high serotonin content of the green banana (matoke) that is eaten as staple food by certain tribes.[77] Although it has been suggested that biochemical and histochemical studies may yield pertinent results in other types of cardiomyopathy, the extensive studies of Bing's group[78] on the coronary sinus have thus far failed to reveal any specific metabolic abnormalities.

F. Congestive heart failure. Low-output failure such as follows valvular disease or hypertension occurs in spite of a normal uptake of substrates and oxygen[79] and in the presence of normal oxidative phosphorylation in mitochondria.[80] Similar work

suggested to Wollenberger that high energy phosphate bond production in cardiac failure was not at fault. Therefore it is commonly accepted that the oxidation of substrates and the formation of ATP are normal in this type of failure; nevertheless recent studies by Bing suggest decreased activities of Krebs cycle enzymes in failing hearts.

The abnormalities of the contractile proteins found in cardiac failure, both animal and human, suggest a defective use of energy as the basic event. Olson[4] found that myosin from failing hearts had a molecular weight three times that of myosin from normal hearts, but this was not confirmed by Davis and co-workers nor by Olson[3] on reinvestigation of the problem. Other protein abnormalities thought to exist in the failing heart are the decreased myofibrillar ATPase activity and the decreased incorporation of sulfur-containing amino acids into myocardial proteins. The major problems in the correct interpretation of these changes are that the methods of protein chemistry are complex and difficult to reproduce exactly and that any such changes could as readily result from as be the cause of myocardial failure. Therefore Mommaerts and Langer have pleaded for a decisive reinvestigation of the possible role of actin and myosin in failure.

G. Death. It seems that the apparent finality of myocardial death is being questioned. Actomyosin bands taken from cadaver hearts up to 6 hours post mortem could contract when ATP was added. Even more dramatic are the findings of Andreev who removed human hearts many hours after death, kept them in vitro at 5 to 10°C for many hours and then restarted activity by a perfusion fluid containing substrate, electrolytes, vitamins, insulin, thyroxine and often plasma. Life of an organ can no longer be equated with life of the whole organism and death may mean something different to biologist, physician and theologian.

Conclusions

The modern trend in the elucidation of the physiologic, pharmacologic and pathologic problems of the myocardium is to rely increasingly upon the techniques of biochemistry and biophysics. Myocardial metabolism may be simplified into the closely associated processes of the production of energy by the breakdown of carbohydrate and lipid substrates and the utilization of energy by the interaction of the contractile proteins.

It is not yet possible to define fully the molecular and submolecular events culminating in cardiac contraction. Therefore descriptions of the influence of various physiologic, pharmacologic or pathologic factors remain incomplete. Among the physiologic factors considered are those maintaining the force of cardiac contractions, variations in heart rate, pH, heart load and temperature, and also the effect of hormones. The pharmacologic stimuli which are reviewed are the cardiac glycosides, reserpine and nicotine. Metabolic factors appear to participate in pathologic processes as diverse as heredofamilial disease, toxic myocarditis, thyroid heart disease, beriberi heart disease, alcoholic cardiomyopathy, idiopathic cardiomyopathy and congestive heart failure.

Two major enigmas are the mode of action of the cardiac glycosides and the metabolic abnormalities basic to congestive heart failure. It is possible that these and related problems will yield only to a concerted study of all the processes involved in the translation of energy from substrates into contraction.

In looking to the future it may be prophesied that the successful application of a technique for direct ventricular biopsy yielding sufficient tissue for chemical analyses by modern micromethods would be a great impetus to unravelling the many problems of human myocardial metabolism in health and disease.

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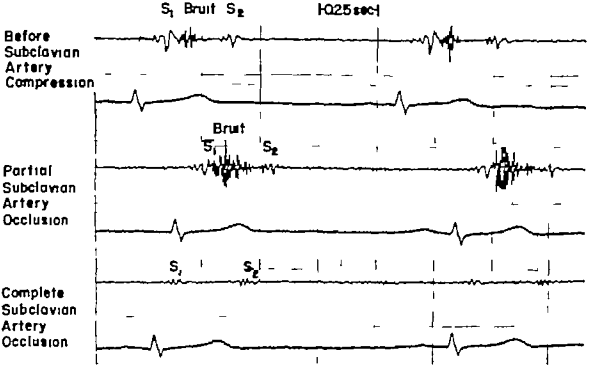


Fig. 2. Phonocardiogram showing a benign supraclavicular arterial bruit in D. G., a healthy 17 year old boy. With partial occlusion of the ipsilateral subclavian artery, the bruit becomes louder and longer. With complete occlusion, the bruit disappears.

of auscultation previously described and of the heart rate and blood pressure. Then the drugs were given subcutaneously. Neither students nor examiners knew which drugs had been given at the time that the observations were made. Four students received 0.3 mg. of levarterenol, 9 received 0.5 mg. of epinephrine, 4 received 0.2 mg. of isoproterenol, and 10 received 50 mg. of ephedrine. Observations of pulse and blood pressure were made at intervals of 3 minutes. When evidence of the effect of the drug upon pulse and blood pressure was observed, auscultation was repeated, and if a supraclavicular bruit was found, the effect upon it of compression of the subclavian artery was determined. Initial examination following the drug was made after 5 to 14 minutes and was carried out until the effect of the drug had begun to subside (33 to 70 minutes after injection).

In selected subjects of Groups 1, 2, and 3, phonocardiograms were recorded in order to determine the time of onset, quality, and duration of the bruit. An electrocardiogram was simultaneously recorded for timing purposes. The phonocardiographs employed were the Schwarzer, the Sanborn Twin Beam, and the 560 series Sanborn Poly Beam photographic recorder. In some instances the record was made as the subclavian artery was compressed.

Results

Group 1. Over a period of 61 months from March 24, 1958, to April 16, 1963, 114 patients were examined. Of these, 10 were found to have murmurs which seemed to arise from supraclavicular bruits (Fig. 1). In these patients the intensity of the murmur in the second right or left intercostal space was from Grade 1 to Grade 3. In 1 patient the murmur was of Grade 1 intensity, in 6 it was Grade 2, in 1 it was Grade 3. In 2 the intensity was not specified. In these patients a diagnosis of aortic or pulmonary stenosis had been proposed. These subjects were 3 to 19 years of age. In 6 subjects the bruits were of Grade 3 intensity or louder. In 2 there were systolic

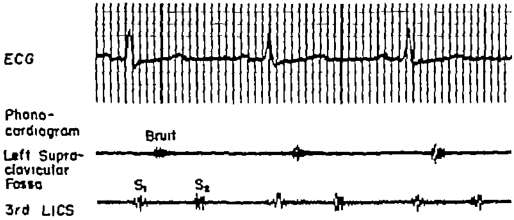


Fig. 4 Phonocardiogram showing the supraclavicular arterial bruit in G. S., a 63 year-old man with anemia whose hemoglobin was 3.8 Gm. per 100 ml. of blood. Note brief duration of bruit and maximum intensity in mid murmur. The bruit disappeared when the hemoglobin was raised to 11.1 Gm. per 100 ml. of blood.

bruits, electrocardiograms were normal in 9*; chest roentgenograms were normal in 9 of the 10—1 had a prominent superior vena cava. Cardiac fluoroscopy was normal in 7 of 8 in whom carried out; the exception was the subject with a prominent superior vena cava. Hemoglobin values were available in 6 subjects and were above 13 Gm. per 100 ml. of blood in each.

Group 2. Of the 179 students, 44.7 per cent had supraclavicular arterial bruits. Of the men, 48.4 per cent had bruits; of the women, 40.2 per cent had bruits. In most they were not loud. Bruits were Grade 2 or louder in 31 per cent and Grade 3 or louder in 5.6 per cent. The bruits were much more common on the right. Bruits were found on the right only in 41 students, bilaterally in 35, and on the left only in 4. In 23 of 80 students, or 28.8 per cent of those with bruits, the murmur could be heard inferior to the clavicle. The effect of compression of the subclavian artery was determined in 66 students. In 54 of these, or 82 per cent, the bruit was eliminated by this maneuver. Only 4 students had a basal systolic cardiac murmur which could have been referred to the neck and supraclavicular fossa. In these 4 it was thought unlikely that the basal murmur was referred to the neck because of the relatively brief duration of the supraclavicular bruit. The effect of posture was evaluated in 38 students with bruits. In 18 the bruit was louder when the subject was in the recumbent position, and in 8 it was louder when the subject was sitting; in 12 students it was of the same intensity in either position. Two students with Grade

*One 17 year-old young woman had [illegible] insufficiency [illegible] electrocardiogram [illegible] patient [illegible] A-V block.

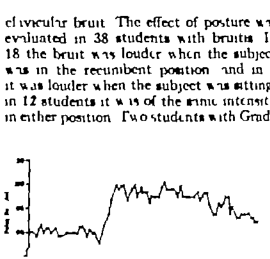


Fig. 5 Appearance of supraclavicular bruit after 0.2 mg. of isoproterenol. Record of change in pulse rate, blood pressure, and appearance of supraclavicular bruit in a 24 year-old medical student. The bruit was of maximum intensity during the peak change in pulse and blood pressure and disappeared as the drug effect subsided.

3 bruits and 1 with a Grade 2 bruit were re-examined within 3 months of the original observations. In 2 the bruit was not found at the second examination.

Group 3. The anemic subjects were 22 to 71 years of age. Their initial blood hematocrit values were 16 to 23 per cent and the hemoglobin values were 3.4 to 8.3 Gm. per 100 ml. of blood. A supraclavicular bruit of Grade 2 or 3 intensity was present in each subject (Fig. 4) except in 1 patient with macroglobulinemia who had an abnormally high blood viscosity. In 3 of the 6 the bruits disappeared as blood hemoglobins were raised from 5.2 to 8.8 Gm., 5.8 to 11.1 Gm., and from 3.4 to 7.3 Gm., respectively.

Group 4. Of 27 students who received sympathomimetic drugs, only 3 had supraclavicular bruits before the drugs were given. Nine developed supraclavicular bruits of Grade II or greater intensity; 4 developed bruits of Grade 3 or greater intensity, including 1 with a Grade 1 bruit initially. Twelve students developed no bruit, and in 2 with initial bruits there was no change. In those with no bruit there was relatively little change in heart rate; the maximum rate was 76 per minute and the maximum increase was 12 heart beats per minute. Of those whose arterial pulse pressure did not increase to 60 mm. Hg or above, or whose pulse rate did not increase at least 15 beats per minute, only 2 developed a bruit. Five students either had a bruit before administration of the drug which did not increase, or developed only a Grade 1 bruit; these were considered to be doubtful cases in terms of drug response. Of 9 students who received epinephrine, 7 developed a supraclavicular bruit, 1 did not, and 1 was a doubtful case. Of 4 students who received isoproterenol, each developed a bruit (Fig. 5). Of 4 students who received levarterenol, none developed a bruit. Of the 10 students who received ephedrine, only 2 developed bruits, 4 did not, and 4 were doubtful cases. Thus isoproterenol and epinephrine, which tend to produce tachycardia, increase arterial pulse pressure, and increase cardiac output, nearly always produced bruits. On the other hand, levarterenol and ephedrine, which usually did not increase heart rate and usually raised diastolic blood pressure, were seldom followed by bruits. In each instance in which a bruit developed, it could be eliminated by compression of the subclavian artery. The bruits in the 13 subjects in whom they were observed were bilateral in 3 and located on the right only in 10. In 4 students it was possible to observe the appearance of a bruit during maximum effect of the drug, and its disappearance as the effect waned (Fig. 5). Unfortunately, some evidence of the effect of drug upon pulse or blood pressure, or on both, was present in the majority of students at the time the observations were terminated.

Discussion

The occurrence of systolic cervical murmurs in apparently healthy subjects was recognized by Arkless,[7] who studied 1,000 men of military age with hearts normal to physical examination and found cervical systolic murmurs in 9.2 per cent. The bruits were much more common on the right, which led the author to speculate that they might arise near the bifurcation of the innominate artery. Exercise was found to increase the intensity of the murmur. Hammond and Eisinger[8] studied 1,000 subjects who were between 2 and 94 years of age and found carotid bruits in 87 per cent of those who were under 5 years of age. The incidence decreased with advancing age, so that by age 60 only 12 per cent had audible bruits. These authors also found that exercise could accentuate or bring out a bruit. They found a 30 per cent incidence of systolic cervical bruits in the age group 20 to 24 years; we found a 44.7 per cent incidence in our study Group 2, composed of freshman medical and nursing students 16 to 28 years of age.

It is of interest that we found only three bruits in the 27 sophomore medical students, an incidence of 11 per cent, which is closer to the figure reported by Arkless. These sophomore students were examined after 30 minutes of rest in the recumbent posture; the freshman students with a 44.7 per cent incidence of bruits were examined immediately after they had entered the examining room. The average heart rate of the sophomore students was 66 per minute and that of the freshman

was 83 per minute. The difference in the means was significant at the $p < 0.001$ level by the t test.[9] Since exercise is known to be capable of bringing out a bruit, the fact that the freshman students had just finished mild exercise probably explained in part the higher incidence of bruits in this group. In addition, increased sympathomimetic activity as the result of greater anxiety was likely.

The phonocardiogram of cervical arterial bruits and the importance of their precordial transmission of these bruits was described by Stapleton and El Hajj. These writers reported 4 patients in [illegible] cervical arterial bruits were transmitted to the base of the heart, resulting in [illegible] erroneous diagnosis of aortic or pul[illegible] stenosis. As in our subjects, the [illegible] later than the [illegible] systolic [illegible] which originate in the aortic or pul[illegible] valves. As in our recordings, the bruit was of diamond shape and of brief duration—less than half [illegible] systole. The bruit was of Grade 3 or 4 peak intensity in the 4 patients described by Stapleton and El Hajj. It seems likely that the cervical arterial bruit described by them is the same as our supraclavicular arterial bruit.

The mechanism and site of production of these supraclavicular arterial bruits has not been established. Our study suggests that the majority originate in the proximal subclavian artery, although some may arise in the innominate or carotid arteries. As pointed out by Stapleton and El Hajj,[8] the short duration of the murmur suggests that it is related to an alteration in blood flow rather than to vascular obstruction, although a very slight obstruction could produce such a brief murmur. Although sympathomimetic drugs may conceivably narrow the subclavian artery, the bruits occurred principally after isoproterenol and epinephrine, which produced tachycardia, increased arterial pulse pressure, and increased cardiac output. That these murmurs can be produced by anemia or sympathomimetic drugs suggests that they are not related to arterial obstruction. Further evidence against an obstructive mechanism is that, on re-examination, a prominent bruit had disappeared in 4 of our subjects and had diminished in a fifth. Several observations suggest that these bruits are related to an increased velocity of cardiac ejection. The production of the bruits with exercise[3] and, in our study, with sympathomimetic drugs is consistent with the concept that increased velocity of left ventricular ejection can produce these bruits. Segal[10] states that the supraclavicular bruit is exaggerated in hyperkinetic states and with aortic insufficiency. The occurrence of these murmurs in anemic subjects with and without increased cardiac output suggests that reduced blood viscosity can cause these bruits in some instances. In this respect our observations may be compared with those of Fisher,[11] who found no cranial bruits in several anemic patients.

One must consider the reason why these bruits are so common in children and in young adults and not so common in older adults. Possible explanations of this frequent occurrence in children and young people are the following. In comparison to adults, children have an approximately 30 per cent greater cardiac output in proportion to body surface area.[1] Children are more likely to be excited during examination than adults. There may be a more rapid velocity of ventricular ejection in young subjects. Weissler and associates[1] found the left ventricular ejection time to be approximately the same in children and in adults with comparable heart rates. However, the possibility of more rapid initial left ventricular ejection velocity is not excluded by these observations. Arteries may be smaller in proportion to blood flow in children; there may be a difference in angulation of the great arteries at the thoracic inlet; arteries are closer to the body surface in children. Other innocent murmurs, such as the cervical venous hum, Still's murmur (vibratory or twanging string murmur), and the pulmonary ejection systolic murmur, are also more common in children. Harris and associates[11] studied the sound frequency envelope of the murmurs of anemia and other high output states and found them to correspond to those of the innocent pulmonary ejection systolic murmur and Still's murmur. The authors postulated that the common innocent systolic murmurs of childhood are caused by the vibration at its natural period of some structure in the

cardiac wall or great vessels arising from the ejection of an unusual volume of blood or the greater velocity of the ejected blood

The benign supraclavicular bruit is of importance because it may simulate the murmur of cardiac valvular disease or arterial obstructive disease when loud enough to be transmitted to the base of the heart aortic stenosis or pulmonary stenosis may be suggested In aortic or pulmonary stenosis the murmur lasts during more than half of systole it is less delayed in onset it is usually louder at the base of the heart than in the neck except in emphysematous subjects Unlike the supraclavicular bruit the murmurs of aortic and pulmonary stenosis are unaffected by compression of the subclavian artery Significant pulmonary stenosis is usually accompanied by expiratory splitting of the second heart sound and a delayed pulmonary closure sound of reduced intensity Significant aortic valvular stenosis is usually associated with a diminished sound of aortic valve closure and at times a single or paradoxically split second heart sound Auscultation of the carotid and vertebral arteries is important in the diagnosis of occlusive cerebrovascular disease [15,16] Ordinarily a cervical or supraclavicular arterial bruit is likely to be benign in a child and is more suggestive of obstructive arterial disease in older adults However as pointed out by Crevasse and Logue [17] cervical murmurs in anemic adults may simulate those which arise from partial obstruction of the carotid artery and Hammond and Eisinger[4] found a 12 per cent incidence of supraclavicular arterial bruits in adults over 60 years of age who had no known cerebrovascular disease The murmurs of carotid artery obstruction are as a rule of greater duration than the benign supraclavicular bruit and with severe obstruction may be continuous In addition unlike the majority of supraclavicular arterial bruits they are unaffected by compression of the subclavian artery A systolic murmur which is produced by partial obstruction of the carotid artery will usually disappear with compression of the ipsilateral carotid artery and will be increased by compression of the contralateral carotid artery The innocent supraclavicular bruit must be distinguished from the organic subclavian arterial bruit which is produced when the subclavian artery is narrowed by atherosclerosis or arteritis [15,17] Here the bruit is usually longer and the blood pressure may be lower in the affected arm The patient may have syncope especially with exercise of the involved arm (subclavian steal syndrome) Radiopaque contrast medium may be injected into the aortic arch in order to visualize its immediate branches however such a procedure is seldom necessary to separate the benign supraclavicular bruit from the murmur of occlusive arterial disease

Summary

1 The supraclavicular arterial bruit is a common normal finding especially so in children and in young adults The bruit may be found in the majority of young children and in as many as 30 to 40 per cent of young adults

2 The mechanism of production of this bruit is unknown In most instances it appears to originate in the proximal part of the subclavian artery whence it is often transmitted to the common carotid artery and the base of the heart The bruit may occur in otherwise healthy subjects who become anemic but in this study it did not necessarily depend upon an increase in cardiac output The bruit could be produced in healthy subjects who were given isoproterenol or epinephrine but usually was not elicited by levarterenol or ephedrine which suggests a relationship to increased arterial flow or to the velocity of left ventricular ejection

3 The supraclavicular bruit is of short duration usually beginning within a few hundredths of a second after the end of the first heart sound in the neck but with a delay of several hundredths of a second after the first heart sound at the base of the heart In most instances the supraclavicular bruit occupies less than half of systole and demonstrates peak intensity in mid murmur (diamond shape)

4 The supraclavicular bruit may suggest aortic or pulmonary stenosis when referred to the base of the heart Its delayed onset its brief duration and its greater intensity in the neck and the effect on it of compression of the subcl

artery will make the distinction clear

5 The supraclavicular bruit may be distinguished from the bruits of carotid artery disease and organic obstruction of the subclavian artery by its relatively brief duration and as a rule by its occurrence in children and younger adults without a history suggestive of impaired cerebral blood flow

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The rationale and methods for combatting hypercapnia in cor pulmonale

M Irene Ferrer M D
Rejane M Harvey M D
New York N Y

Cor pulmonale (pulmonary heart disease) is most commonly produced by a disordered gas exchange that results in hypoxia and hypercapnia. A wide variety of disturbances in pulmonary function and/or anatomy may induce abnormalities but most common among them are the obstructive diseases of the lung, notably bronchitis, bronchiolitis and emphysema.

The role of hypoxia as a major determinant of pulmonary hypertension, polycythemia and hyperkinetic blood flow is well established. Furthermore the reversibility of these phenomena with improvement in gas exchange is accepted. Recently the hemodynamic importance of hypercapnia has been identified by the demonstration that an increase in blood hydrogen ion concentration (a lowering of pH) can increase pulmonary arterial pressure and augment the pressor response to hypoxia.[1]

Two other serious complications of chronic hypercapnia and the resulting acidosis are now known. One is the production of symptoms in the central nervous system such as restlessness, asterixis, twitching, ocular chemosis, paranoia, insomnia, headache and coma. The other is the altered ventilatory response to inspired gas mixtures high in oxygen. For a number of years it was thought that patients with hypercapnia who demonstrated a decrease in ventilation on exposure to gas mixtures high in oxygen did so because of a loss of sensitivity to carbon dioxide as a respiratory stimulus. It was assumed that the major drive to ventilation stemmed from oxygen want and if this was satisfied ventilation would diminish. However acute exposure of patients with hypercapnia to 3 per cent CO_2 has indicated firstly that these patients do increase their ventilation but do so in a subnormal fashion. Secondly the limitation of their response originates in part from a mechanical source, i.e., a marked increase in the work of breathing beyond which they apparently cannot go.[2] The exact role of the sensitivity of the medullary centers to the elevated molecular CO_2 remains uncertain in this type of patient.

It is clear however that a patient with chronic hypercapnia hypoventilates when

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Cardio-Pulmonary Laboratory of the First Medical Division and the Chest Service, Columbia University Division, Bellevue Hospital, New York, N. Y.

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Address: Cardio-Pulmonary Laboratory, First Medical Division, Bellevue Hospital, New York, N. Y. 10016.

exposed to an increased concentration of oxygen, although the exact mechanism whereby this occurs is unknown. The marked diminution in ventilation constitutes a major hazard since it furthers the retention of carbon dioxide and acidosis.

The major therapeutic challenge in these individuals lies in improving oxygen saturation and simultaneously reducing the level of carbon dioxide. This can be achieved in a number of different ways. Foremost among them is the use of antibiotics to suppress the exudates and secretions consequent to infection which clog the tracheobronchial tree. This, coupled with tracheal suction and adequate hydration, is extremely effective in furthering alveolar ventilation. The systematic use of vaporized bronchodilators, particularly if administered with a positive pressure apparatus which disseminates the aerosol, reduces mucosal edema and bronchial obstruction, thereby augmenting the number of units effective in gas exchange. The use of these bronchodilators may be associated with an increased production of sputum as ever increasing numbers of bronchi and bronchioles are able to disgorge their contents. Positive pressure breathing using moist air interchangeably with bronchodilators is very effective in hyperventilating these subjects and should be employed as continuously as possible. With every effort being bent to clear the tracheobronchial tree and promote ventilation, it is obvious that smoking, which is a powerful irritant that results in bronchorrhea, is contraindicated. Similarly, the suppression of cough by drugs or the use of narcotics, tranquilizers, or barbiturates with their attendant respiratory depressant effect cannot be condoned.

In a certain number of individuals the severity of the hypoxia demands immediate administration of oxygen. This can be accomplished in a number of ways. The patient can be placed in a tank respirator and given oxygen by nasal catheter. The respirator is usually effective enough to maintain ventilation despite the increment in inspired oxygen. Those patients who cannot tolerate the tank respirator should be removed from it and provided with tracheal intubation. The endotracheal tube is then attached to a positive pressure apparatus with an automatic cycling device and an oxygen enriched mixture is administered. We have not found it necessary or desirable to institute tracheostomy in these patients.

Frequently, when the acute episode is terminated, one finds that the patient's blood oxyhemoglobin saturation has risen to satisfactory values (88 to 90 per cent), but that hypercapnia persists, albeit at a lower level (pCO_2 of 48 to 58 mm. Hg). If infection and bronchial obstruction continue to be adequately treated, the residual hypercapnia can be reduced successfully by prolonged use of the mechanical aids to ventilation. These subjects are known to hypoventilate when asleep. This can be combatted by the use of a tank respirator during the night hours. The use of a positive pressure apparatus for 6 to 8 hours during the day can also net sufficient hyperventilation to diminish hypercapnia. With either the tank respirator or the positive pressure unit it is not necessary or desirable to administer oxygen. It had been hoped that the carbonic anhydrase inhibitors would promote more effective elimination of carbon dioxide, but the associated metabolic acidosis which they induce limits their usefulness.

Restriction of activity cannot be overemphasized as a major therapeutic measure in the care of these patients, not only in their acute episode but also while they are convalescing. During exercise, saturation falls and carbon dioxide tension rises. For these individuals who are laboring toward effective gas exchange, the additional burden of work should be removed.

The best means available at this time for judging whether any of these therapies is successful is a determination of the arterial blood oxygen saturation and carbon dioxide tension. During the acute phase of cardiopulmonary insufficiency, such measurements may be required daily. Once definite improvement has occurred, determination of blood gases is necessary whenever major changes in therapy have been instituted. Attempts to treat cardiopulmonary insufficiency without measurement of the blood gases are as illogical as treating diabetic or renal acidosis without reference to the level of blood sugar or the serum electrolytes.

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Alcohol and the heart

Alcohol has long been used in the treatment of angina pectoris almost as effective as nitroglycerin in preventing the angina induced by standard exercise alcohol does not prevent or modify the transient electrocardiographic manifestations of myocardial ischemia as do the nitrates The symptomatic relief afforded by alcohol in the anginal syndrome is apparently mediated by tranquilizing psychic influences rather than by [illegible] coronary vasodilator action

Although chronic alcoholism may exert a protective effect on the body with respect to the development of atherosclero[illegible] a view not held by all investigators [illegible] the adverse metabolic effect on the liver militate against excessive and prolonged consumption of alcohol [illegible] the prophylaxis of coronary artery disease Furthermore nutritional deficiencies associated with chronic alcoholism may induce concomitant myocardial damage [illegible] Evans has defined characteristic abnormalities of the electrocardiogram in chronic spirit-drinkers with symptoms referable to cardiac involvement He considered alcoholic cardiomyopathy as a specific histopathologic entity to be distinguished from the alcoholic beriberi syndrome [illegible] Elhaser and Gian[illegible] divided the clinical cardiac manifestations of chronic alcoholism into three categories (1) alcoholic myocardosis (without vitamin deficiency) (2) nutritional heart disease (with hepatic insufficiency) and (3) beriberi heart disease Burch and Walsh have reviewed the possible role of multiple subclinical nutritional deficiencies in the genesis of cardiac insufficiency in the chronic alcoholic

Perhaps less well known are the cardiovascular reactions resulting from acute alcoholism Over indulgence according to White may produce neurocirculatory asthenia paroxysmal arrhythmias an increase in angina pectoris or precipitation of congestive failure in cardiac patients Progressively rising concentrations of alcohol in the blood cause tachycardia and systemic arterial hypertension followed by bradycardia hypotension and ultimate asystole which is the consequence of asphyxia rather than a direct myocardial effect [11] Our experience has shown that acute alcoholic intoxication in persons with established coronary atherosclerosis may occasionally provoke an episode of fatal coronary insufficiency

The recent necropsy files of the Ottawa General Hospital record 2 cases of sudden death in markedly intoxicated individuals with nonocclusive coronary artery disease A 34 year old man collapsed and died while riding on a bus Autopsy disclosed a 400 gram heart with segmental atherosclerotic narrowing of the major coronary arteries but no myocardial lesion The postmortem level of alcohol in the blood was 300 mg per cent The second man who was 65 years of age dropped dead unexpectedly at home His heart weighed 430 grams and the coronary arteries were markedly atherosclerotic but patent Only a few small patches of scar tissue were noted in the myocardium The level of alcohol in the blood was 240 mg per cent Both victims were well nourished and had fatty livers there was no evidence of fat embolism or of chronic congestive heart failure The mode of death in each instance was not that of ethanol poisoning with respiratory depression and deepening coma

Presumably the potent vasodilating effect of alcohol on the peripheral arteriolar bed transiently reduces coronary blood flow enough to cause relative myocardial ischemia in the presence of coronary atherosclerosis In concentrations greater than 100 mg per cent alcohol may have an actual vasoconstricting action on the coronary vessels [12] In addition it has been shown that infusion of alcohol causes a pronounced increase in oxygen consumption by the myocardium [14] These factors offer a satisfactory explanation for the occurrence of sudden death in drunken persons with nonocclusive coronary artery disease and may contribute to the pathogenesis of so-called alcoholic cardiomyopathy in chronic inebriates

H Alexander Heggtveit M D
Departments of Pathology
Ottawa General Hospital and
Faculty of Medicine University of Ottawa
Ottawa 2 Ontario Canada

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Arm versus forearm blood pressure in obesity

There has been an uninterrupted stream of notes on the indirect determination of arterial blood pressure since the inception of this technique as a clinical tool. Many of these reports have not indicated knowledge of prior work in this heavily explored field; many have provided inadequate supporting data for the various conclusions and recommendations, and few have employed the randomized methods of study necessary to a proper evaluation of the results.

Original and useful propositions for indirect measurement are rare but it is worth while to continue the search. The clarification of problems and the standardization of method in the indirect technique are particularly needed in population studies in which variability of the measurement and small systematic errors significantly influence the comparisons and interrelations derived.[1-4]

A recent note proposes without evidence the use of forearm indirect blood pressure as a more valid representation of true arterial pressure than upper arm readings in obese subjects. This has actually been studied in some detail previously.

Ragan and Bordley[4] found small but significant differences between indirect values from auscultation over the radial artery, cuff on the forearm, and conventional arm measurement (6 mm Hg lower systolic in forearm and 6 mm Hg higher diastolic). They found much lower forearm pressures in 3 grossly obese subjects (60-140 mm Hg systolic, 20-85 mm Hg diastolic). In a careful comparison between hypertensive patients and normal subjects Trout and associates found forearm indirect readings more representative of direct arterial pressure than the arm pressure in very obese persons. Berliner and associates found that the conventional arm indirect measurement overestimated true systolic pressure in 39 of 61 obese subjects as well as in 26 of 39 nonobese subjects. In 8 of 10 of the fattest subject the arm pressure was an overestimation.

Because of these observations the Beaconsfield Conference of Longitudinal Cardiovascular Study Groups[4] recommended in 1957 an investigation of the blood pressure in forearm and upper arm in relation to estimated fatness leading to recommendation on the use of forearm measurements.

A systematic study of arm-forearm indirect pressure in 76 middle-aged men was recently made in this laboratory. The concern here was whether the forearm technique should be considered for broad population studies. It was found that the Korotkoff sounds were inaudible at the radial artery cuff applied to the forearm in 16 of the 76 men (21 per cent). The median systolic indirect pressure of 60 men was 124.5 mm at the brachial artery and 124 mm at the radial artery; the diastolic pressure was 79 mm at the brachial artery and 87.5 mm at the radial artery. The onset of systolic sounds was heard at a lower level in the forearm in 38 of 60 comparisons, whereas the forearm diastolic phase were heard at a higher level in 47 of 60. The difference between arm and forearm indirect pressures was unrelated to the circumference of the arm or thickness of skinfold (obesity) throughout the bulk of the distribution of the variables. The three largest arm-forearm discrepancies occurred among the 8 men with the largest fattest arms, the forearm value being 20 to 38 mm lower systolic. However, the difficulty in obtaining the radial forearm pressure in all subjects and the lack of security about the superior validity of forearm pressure in any subject preclude serious consideration of the technique in the measurement of blood pressure in fat hypertensive subjects found in population studies.

In the clinic more care in the application of the standard 12 by 23 cm cuff is required. There is in addition good evidence that a 14 by 40 cm cuff reduces the random error in indirect measurement and results in less systematic error for the extremely obese arm. In the unusual circumstance of serious doubt whether an individual patient has important

elevation of blood pressure intra arterial pressure should be measured

Henry Blackburn M D
Jaako Kihlberg Ph D
Joseph Brozek Ph D
Laboratory of Physiological Hygiene
University of Minnesota School of Public Health
Minneapolis Minn 55455

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Sodium concentration and electrical resistance of renal tissue

Under normal conditions due to the countercurrent multiplier mechanism operating in the loops of Henle of the renal medulla an increasing concentration of sodium from cortex toward the papilla is seen The maintenance of this medullary hypertonicity partly depends upon the flow of blood through the vasa recta which act as countercurrent diffusion exchangers An increased rate of medullary blood flow would reduce medullary sodium concentration whereas a decreased flow would exert an opposite effect

To our knowledge there is no method for measuring the concentration of sodium in renal tissue in vivo So far tissue sodium has been determined with a flame photometer in vitro after kidney slices have been digested in a mixture of concentrated sulfuric and nitric acid

On the basis of the fact that an inverse relationship exists between sodium concentration of a medium and its electrical resistance a new method has been devised in our laboratory for estimating changes in the concentration of sodium in renal tissue in the living animal by measuring changes in renal electrical resistance

Rats which weigh between 200 and 250 grams are anesthetized with sodium pentobarbital 10 5 mg given intraperitoneally then a midline abdominal incision is made and both kidneys are exposed Two specially made needle electrodes with pointed ends are placed on a stand 4 mm apart from each other and are connected to an impedance bridge The electrodes are inserted from the cortex inward to the medulla and papilla by utilizing a micromanipulator connected to a micrometer

Through the use of the smallest possible bridge voltage (less than 50 millivolts) in order to avoid tissue damage and minimize electrode polarization the electrical resistance of the renal tissue between the two electrodes is measured at depths of 1 3 and 5 mm from the surface of the kidney These distances are taken arbitrarily as representing the approximate mid points of the cortex medulla and papilla respectively Thereafter the renal pedicles are ligated and the kidneys are quickly removed and divided into cortical medullary and papillary portions Subsequently after the separated tissues are weighed and digested for at least 48 hours in a mixture of concentrated nitric and sulfuric acid the concentration of sodium is measured by a flame photometer and is expressed in microequivalents per gram of wet tissue Following this a correlation is made between changes in electrical resistance and the concentration of tissue sodium in the various compartments of the kidney under normal conditions and after the injection of renal vasoconstrictors and vasodilators

In a series of 25 experiments a good inverse relationship between the sodium concentration and

electrical resistance of renal tissue was seen. Through the use of electrodes of varying length and diameter it was established that (1) The concentration of sodium progressively increases from cortex to inner medulla (papilla)[1-4] whereas electrical resistance progressively decreases. (2) Medullary and papillary concentrations of sodium and electrical resistance could be significantly altered by the renal vasodilator hydralazine without any essential cortical changes.

It should be mentioned that although there is an inverse relationship between electrical resistance and sodium concentration, the resistance is also affected by other ions.

Through utilization of this method the following objectives may be achieved: (1) Dynamic changes in the concentration of sodium in any portion of the renal cortex and renal medulla of the living animal can be estimated by measuring change in tissue electrical resistance. (2) Since an inverse relationship exists in the renal medulla between blood flow and sodium concentration, and also since it has been demonstrated herein between electrical resistance and sodium concentration, change in medullary electrical resistance should be directly related to alterations in medullary blood flow. Therefore after the administration of various vasoactive substances, we should be able to estimate alterations in medullary blood flow by measuring change in medullary electrical resistance.

Ignatius J. Voudoukis, M.D.
Clifford L. Nelson, Ph.D.
Cardiovascular Research Laboratory
Maine Medical Center
Portland, Me.

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Present address: Division of Hypertension, Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, Mich. 48202.

Heart preservation utilizing hyperbaric oxygen and hypothermia

One of the major limitations to homologous organ transplantation today is the unavailability of the organ for implantation. The immunological rejection problem has not been satisfactorily approached or solved, but possibly this will be controlled so that homologous organ transplantation will be clinically applicable in certain selected clinical states.

Attempts at organ storage have been shown by Shumway to be feasible. After storage for 7 hours in iced saline solution, homologous transplanted hearts have remained functional up to 21 days and autogenous transplanted hearts are functional at 2 years.

An additional approach to preservation has been that of utilizing hyperbaric oxygen at 3 atmospheres and hypothermia of 2 C. Our success with this technique of heart storage for periods up to 24 hours has shown that organ storage is possible.

The technique involved necessitates hypothermia to 25 to 30 C by surface cooling of the donor animal before removal of the heart. The heart is removed within 2 to 4 minutes after ligation of the superior and inferior venae cavae, all the pulmonary veins, the pulmonary artery, and the aorta with its branches. The heart is immediately placed in the hyperbaric oxygen chamber in either sterile lactated Ringer solution or normal saline at a temperature of 2 C. The 2 C temperature is maintained and the pressure in the chamber is raised to 4 atmospheres of 100 per cent oxygen. It is necessary to monitor the chamber constantly so that the temperature does not drift below 2 C and cause freezing of the tissue which destroys the myocardium. The hearts are preserved in the chamber for 24 hours, removed, and reimplanted into the neck of a recipient animal. The aorta is anastomosed to the distal carotid artery, the proximal carotid artery is anastomosed to the left appendage to supply blood to the heart, and the pulmonary artery is anastomosed to the proximal jugular vein. To re-establish circulation the heart must be ... massage is necessary until the heart warms and starts fibrillating. The heart is defibrillated and is active in the recipient's neck with normal sinus rhythm.

By means of this technique, 5 per cent of the hearts stored for 24 hours and transplanted have responded to defibrillation with a normal sinus rhythm. Our observations at this time have not

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determined how long the preserved heart will maintain the circulation. Surgical technique is no longer a limiting factor in homologous organ transplantation. Organ preservation may be solved, which will leave only the rejection phenomena as the major problem. If the rejection phenomena is solved in the future, one might anticipate the development of transplantation organ banks.

Even if this technique of heart preservation does not develop into a clinically applicable technique in the near future, it is interesting that an organ as complicated as the mammalian heart may be removed from an animal and be stored for 24 hours and that it will then resume normal sinus rhythm when implanted in a recipient.

Carl H. Almond, M.D.
Hilario Anido, M.D.
Anthony Seaber
Ross Young, M.S.
James W. Mackenzie, M.D.
Department of Surgery
Section of Thoracic and Cardiovascular Surgery
University of Missouri School of Medicine
Columbia, Mo. 65202

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Special report

First International Conference on Preventive Cardiology, August 24-28, 1964

Summary by W. Raab, M.D.
Burlington, Vt.

An appeal directed to governmental and private health agencies and foundations in industrialized, prosperous, heart disease-ridden countries, and signed by 120 participants in the First International Conference on Preventive Cardiology, which was held in Burlington, Vermont, under the auspices of the University of Vermont, contains the following paragraphs:

The Conference has made an effort to gather and to integrate pertinent but previously very poorly coordinated and utilized basic and clinical information from many lands into a scientifically sound pattern of preventive reasoning as the understructure for rational and determined preventive action.

In old age, cardiac death is not the worst of alternatives, but it must no longer be permitted by responsible health agencies to destroy countless creative, useful lives without being faced by energetically guided attempts at rational preventive counteraction. Belated therapy and rehabilitation, no matter how ingeniously devised and carried out, are no adequate solution of the problem.

The United States of America is among all nations the one that suffers from the highest uncontrolled premature mass mortality from cardiac causes, notably ischemic heart disease. Paradoxically, in the face of their unparalleled contributions to curative medicine and entirely fascinated by its triumphs, the medical profession and health authorities of the United States have not yet undertaken or planned any organized large-scale preventive action against ischemic heart disease, except for official warnings against smoking and the excessive consumption of fat.

The reasons for this reluctance may be attributed chiefly to (a) unfamiliarity with much of the extra-American literature on cardiac pathophysiology and with the vast European preventive heart reconditioning systems, (b) a sophisticated rejection of any primarily empirical measures, and (c) a traditional but no longer tenable uncritical identification of ischemic heart disease with coronary atherosclerosis and its implications of a limitation of oxygen supply, while the logically inseparable pathogenic corollary, namely the wide fluctuations in the neurohormone-dominated consumption of oxygen by the myocardium, is widely disregarded.

The subject of potentially pathogenic neurogenic (= neurohormonal) interferences in myocardial metabolism, function, and structure, and their preventability, was therefore placed at the top of the agenda by the organizer and chairman of the Conference, W. Raab, whereas the already massively explored problems of atherogenesis were deliberately excluded despite the obviously pre-eminent con-

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Address: The Preventive Heart Reconditioning Foundation, [illegible] Burlington, Vt.

tributory role of coronary atherosclerosis in the etiology of ischemic heart disease Accordingly only two reports were devoted to current attempts at planning preventive action against pluricausal ischemic heart disease in the U S A from the aspect of its vascular component through dietary measures I H Page (represented by R B McGandy U S A) surveyed the present status of the preliminary feasibility study to evaluate the prospects of a large scale fat reduction experiment in the American population J Stamler (represented by H A Lindberg U S A) discussed a promising educational program of the Chicago Board of Health to modify dietary as well as smoking and exercise habits

Proceeding step by step through outwardly disconnected yet in one way or another prevention related fields of medicine (cellular chemistry pathophysiology pharmacology pathologic morphology clinical cardiology psychology epidemiology sports medicine sociology professional and lay education) the agenda of the Conference were arranged in such a fashion as to establish a logical chain of reasoning ...nately pointing to the needs and possi...ties of positive practical preventive action

Rapidly developing upheavals in the myocardial distribution of electrolytes and enzymes hypoxic electrocardiographic patterns subendocardial hemorrhages and multifocal necrotic destruction of tissue (microinfarcts) were reported resulting from injections of adrenergic cathecholamines (T J Regan E Bajusz and W Raab U S A) from electrical stimulation of the hypothalamus (I K Melville Canada) or of the cardiac sympathetic nerves (M A Klouda and W C Randall U S A) from catecholamine liberating emotional (McF Groover and W Raab U S A) and physical stresses (N N Kipshidze U.S.S.R) in animals and from the administration of catecholamine liberating nicotine (S Bellet and D G Wenzel U.S.A) H Selye (Canada) described a marked potentiation of the myocardial necrotizing toxicity of both injected and stress liberated catecholamines by adrenal corticoids and certain sodium salts

On the clinical level an augmentation of the urinary excretion of catecholamines under emotional tension as contrasted with a reduction in catecholamines by the viewing of idyllic nature films was reported by L Levi (Sweden) R Starcich (Italy) and J A Richardson (U S A) presented data on characteristically exaggerated elevations of serum catecholamines under physical and emotional stress in patients suffering from angina pectoris Abnormally high blood levels of catecholamines in patients with congestive heart failure were observed by C H Chidsey and associates (U S A) whereas the concentration of catecholamines in the damaged failing heart muscle itself was found to be diminished by these investigators

The influences of altitude and climate (heat and humidity) on autonomic nervous manifestations and on the clinical condition of cardiac patients were the subject of presentations by M Halhuber (Austria) and G E Burch (U S A) respectively G C Griffith (U S A) called attention to various still problematic alterations in the metabolism of the aging heart muscle

Strong emphasis was placed on the role of emotional factors in the origin of ischemic heart disease and in its possible prevention V Lapiccirella (Italy) reported on neurogenic electrocardiographic changes under emotional stress and on the low incidence of ischemic heart disease among primitive Somali nomads with a relatively tension free life who consume animal fats in abundance but exhibit a low urinary excretion of catecholamines Similar conditions were found according to S Wolf (U S A) in a patriarchal American settlement of Italian immigrants from Roseto who maintained the cheerful unsophisticated habits of the old country By contrast a strikingly excessive morbidity from ischemic heart disease was ascertained by large statistical studies among persons displaying traits of high strung ambition time urgency and restlessness (R H Rosenman and associates U S A) and among those engaged in emotionally and mentally stressful occupations for example physicians in general practice as compared with dermatologists and pathologists etc (H I Russek U S A) The potentially pathogenic significance of inescapable crushing

emotional nutcracker situations was pointed out by J B Wolffe (USA) and their abnormal electrocardiographic equivalents by L H Sigler (USA) S Minc (Australia) discussed the possible detrimental effects of civilization-dictated deliberate muscular motions without appropriate emotional trigger motivations in promoting neurogenic cardiac disorders

Impressive evidence for an important contributory involvement of heavy tobacco smoking in the origin of ischemic heart disease evolved from the statistical studies of J T Doyle (USA) A large mass of epidemiologic studies concerning an apparently powerful contributory influence of sedentary living on the morbidity and mortality from ischemic heart disease has accumulated during the last decade The investigations of D Brunner (Israel) stand out because of the unusual racial environmental and nutritional uniformity of his subject material in communal settlements C G Hames and associates (USA) furnished data on the cardiac ischemic morbidity both in Negroes and in persons of different social and occupational strata in the state of Georgia leading to the same conclusion namely that a lack of physical exercise appears to be a potent factor in the development of hypokinetic diseases as defined by H Kraus (USA)

The underlying autonomic nervous derangements namely a deficiency of vagal and sympathoinhibitory counterregulation against exaggerated sympathoadrenergic preponderance in cardiac function and metabolism in physically inactive individuals were reconfirmed by W Raab and H J Krzywanek (USA) who taking also emotional personality patterns into account demonstrated a new potential cardiac predisposition risk test based on direct measurement of the cardiac sympathetic resting tone and stress response for application in prospective epidemiological studies Another epidemiological cardiac fitness test involving exercise and heart rate is being developed by C C Allard and associates (Canada)

Interesting relationships between a low vital respiratory capacity physical inertia and proneness to cardiac ischemia were revealed by T J Dawber (USA)

After an exposé by G Schimert (West Germany) explaining the inseparable interdependence of the vascular mechanical and myocardial oxidative components of coronary reserve and of its optimal preservation by physical training the Conference reached its climax by offering a group of reports that dealt with objective effects on cardiac functional parameters and working capacity which resulted from extended periods of physical training in pre morbid and supposedly cardiac ischemia prone persons as well as in manifestly stricken patients Several exercise programs adjusted to the individual state of health and fitness carefully graded and supervised were carried out on sizable numbers of subjects by H K Hellerstein J Naughton E Jokl V Smodlaka (USA) H Mellerowicz (West Berlin) and M Wasserman (Israel) with nearly uniformly favorable results These concerned apart from an ameliorated subjective well being an objective reduction in the cardiac sympathetic resting tone and excitability an improvement in the respiratory vital capacity and to some extent in electrocardiographic anomalies A lowering of elevated levels of blood pressure and blood cholesterol was also observed T K Cureton (USA) insisted that exercise programs in order to produce valuable cardiac effects must attain a certain degree of vigor and must be pursued persistently Demonstration of preventive and therapeutic exercises was given by T K Cureton without equipment and by D Schmidt Dincklage (West Germany) with the Bali device

A complete novelty for most of the participants in the American Conference were brief reports on the organization financing and operational programs of the nearly 3 000 government sponsored preventive rural reconditioning centers (kurorts) dispensaries and night sanatoria in the Soviet Union (A L Myasnikov USSR) in other eastern European countries (J Badal Czechoslovakia) and in the Alps (P Beckmann and O Bruns West Germany) Switzerland Austria etc On an originally empirical basis these centers are aimed at the three elementary goals of the prevention of ischemic heart disease (1) environmental-emotional relaxation (2) systematic physical train

ing, and (3) indoctrination of life-long maintenance of health habits acquired at the centers.

Measurements of various parameters of cardiovascular function before and after 4 weeks of reconditioning period, in German and Austrian centers, were reported by H. W. Kirchhoff, M. Blohmke (West Germany), and H. Marchet (Austria). They showed again a significant diminution in the cardiac sympathetic resting tone and in its excitability under physical stress, as manifested by lowered heart rates and prolonged isometric contraction period of the left ventricle, plus an enlarged pulse pressure on tilting into the upright position.

The most conspicuous weakness of the Conference and of the present state of affairs consists in the lack of direct epidemiological proof of the preventive effectiveness of any of the measures discussed.

Controlled statistical data are now being collected in West Germany over a 5-year period. Nevertheless, a general consensus of opinion emerged to the extent that, aside from the obvious desirability of more conclusive early risk testing and conditioning studies (A. Kagan, World Health Organization, Switzerland), sufficient basic and indirect clinical information on the preventability of ischemic heart disease is already at hand to warrant early, determined, and as far as possible internationally coordinated positive preventive action.

H. Schaefer (West Germany) and K. J. Slater (U.S.A.) emphasized the still existing inadequacies with regard to the social and preventive aspects of training in the medical schools and the need for much greater interdisciplinary cross-fertilization and integration. A concluding message from P. D. White (U.S.A.), the patriarch of American cardiology, stressed the moral obligation of the medical profession to practice what we preach.

An optimistic note was sounded by President Lyndon B. Johnson of the United States, who is himself a fully rehabilitated victim of ischemic heart disease. In a welcoming letter addressed to the Conference, he stated that "prevention is the greatest of all goals in man's long struggle to conquer disease, and preventive cardiology is steadily bringing us closer to that goal in an area of major health concern."

Letter to the Editor

Iowa State University
of Science and Technology
Ames, Iowa 50010
June 9, 1964

To the Editor:

This letter is in response to the editorial entitled "The Advantages of Research on Man," which appeared in the March 1964 issue of this JOURNAL.

I should like to concur with the major tenet of the editorial that as much medical research as can be readily and ethically accomplished which is for the benefit of man be performed upon man. However, my purpose in writing is to set down thoughts about animal experimentation and about research in general which were evoked while reading this paper.

In those investigations utilizing experimental animals in which the prime goal is to discover information useful for application in man, a major prerequisite should be to minimize those factors, outside of species anatomical and functional differences, which would exaggerate experimental results and thus decrease the validity of extrapolating information back for application in man. It is important to work with animals which are normal (for the species) and in a prime state of health. Additionally, the experimental conditions ideally should be designed so that the only influence is the variable which is being studied. As is commonly the case, extraneous factors such as concurrent disease (infectious, nutritional, or metabolic) and stressful restraint, anesthesia, and surgery obliterate experimental findings.

There are two disciplines which I believe can help to minimize the unwanted factors listed above.

One of these areas is laboratory animal medicine. Increasing numbers of veterinarians find the greatest challenge of their professional career in this field. By virtue of their professional training, they are admirably qualified in comparative anatomy, physiology, pathology, and epizootiology. Many of those who choose careers in this field of research are filling in the great gap in knowledge about the normal state of laboratory animals and about the diseases common to them. Through their training and experience they know the species of their patient and can interpret subtle changes just as the physician detects slight differences in the state of his patient. From their ranks veterinarians who are getting degrees in laboratory animal care are uniquely qualified to practice preventative medicine in supervising the rearing of animals for research.

The second area which is contributing to medical research is biomedical engineering. Again, several aspects of another multifaceted field are potentially of great benefit to medical research. Since discrimination and extrapolation are required to adapt information taken from animal experimentation for use on man, these entail that optimum inductive methods be employed. The use of engineering analytical techniques to examine the function of body subsystems has shed new light on biological control mechanisms. Proof of validity of this approach is continually accumulating. Points of similarity between physical systems and biological subsystems are that both are complex, consisting of many components which are complexly interrelated, and that the function of each is synchronized with the activity of coexisting mechanisms. The judicious application of those methods first designed for evaluating the function of inanimate systems and then adapted for use in medical research promises to quantify pathophysiological responses in any species and also to help in extrapolating results from experimental animals to man.

Biomedical engineering also contributes in the field of instrumentation. Advances in methods and equipment for medical measurement have resulted when the problems encountered by biological research workers are translated into specifications which can be understood by engineers and designers. In recent years the cross training acquired by engineers and biologists in the field of biomedical engineering has expedited and increased the development of medical diagnostic, therapeutic, and research equipment.

As you can see, my comments condense down to the idea that much useful information for the benefit of man is potentially available from animal experimental research. All those who conduct animal experimentation should operate under the precept of obtaining the maximum amount of accurate, relevant data. Four very important ways to achieve this goal are to use healthy experimental animals, to use the best available talent in evaluating responses to experimental treatments, to use optimum instrumentation, and to employ the most valid and illuminating methods for processing experimental results. In order to help achieve this goal, the utilization of the unsurpassed capabilities of the veterinary specialist in laboratory animal medicine and the biomedical engineering specialist should be endorsed. The inclusion of these individuals as collaborators on research teams can greatly benefit health related research.

Neal R. Cholvin, D.V.M., Ph.D.
Professor and Biomedical Chairman
Biomedical Engineering Program

Book reviews

HYPERTENSION. VOL. XII. BLOOD PRESSURE AND TOXEMIA OF PREGNANCY. Edited by Simon Rodbard, M.D., City of Hope Medical Center. New York, 1964, American Heart Association, Inc. 95 pages. Price $7.50.

This volume contains the Proceedings of the Council for High Blood Pressure Research of the American Heart Association which met in Cleveland on November 15 and 16, 1963. It is a good review of the subject of blood pressure and toxemia of pregnancy and should be of interest to cardiologists, general practitioners, and physicians as well as obstetricians and gynecologists.

ANGEBORENE HERZFEHLER: AUSKULTATION, PHONOKARDIOGRAPHIE UND DIFFERENTIALDIAGNOSE (Congenital Heart Disease: Auscultation, Phonocardiography, and Differential Diagnosis). By Dieter Michel, Dr. Med., Apl. Professor der inneren Medizin, Universität München. Berlin, 1964, Springer Verlag. 307 pages.

In his 302 page monograph, Michel attempts to present the auscultatory and phonocardiographic findings in various congenital heart diseases and to correlate these findings with underlying anatomical and hemodynamic changes.

After a very brief general review of heart sound and murmur, including the so-called innocent murmur, the author discusses the auscultatory and phonocardiographic findings in specific congenital heart diseases.

In each condition he first reviews the anatomic basis and then discusses the heart sounds and murmurs, the alterations produced by associated anomalies, the postoperative findings, and the significance of hemodynamic changes in the production of auscultatory findings.

Toward the end of the monograph there are tables of differential diagnosis of murmurs (systolic, diastolic, continuous) that occur in various congenital heart diseases. The references are up to date and are grouped according to topic. An index is included at the end of the book.

The format of the monograph and the reproductions of pictures and tracings are excellent. One noteworthy aspect of the phonocardiograms is the use of filters for the recording of sound and murmurs of various frequencies. The only reference used with the phonocardiograms is electrocardiographic Lead II. Their value would have been increased markedly by including other references such as carotid pulse recording, apex cardiogram, etc.

In spite of the above-mentioned shortcomings, the monograph contains valuable information which should prove useful to the clinical cardiologist.

I AM A CHRONIC CARDIAC. By Lynn Fool. New York, 1964, Dodd, Mead and Company. 150 pages. Price $3.75.

This book, written for the layman in an easy to read style, relates the experiences of the author in battling, accepting, and finally adjusting to three coronary attacks. He relates in detail the psychological effect of the disease he went through them and how he intelligently confronted them. He also describes the difficulties of rehabilitation and the value of an intelligent wife throughout these experiences. A broad look into his sense of value and philosophy of life (which this reviewer shares) is provided in a chapter in which accurate data and information on important aspects relating to coronary heart disease are also given. No doubt the wide and varied experience of the author in dealing with people sick and healthy and his background in public relations make this book good reading even for physicians.

PARASITES OF THE HUMAN HEART. By B. H. Kean, M.D., F.A.C.P., Associate Professor of Medicine, Cornell University, Ithaca, N. Y., and Roger C. Breslau, M.D. New York, 1964, Grune & Stratton, Inc. 186 pages. Price $5.

This is an interesting book which summarizes present-day knowledge on parasitic diseases of the heart. The authors describe briefly the pertinent data in amebic pericarditis, balantidiasis, leishmaniasis, Chagas' disease, trypanosomiasis, malaria, toxoplasmosis, paragonimiasis, trichinosis, and many others. The book is well written, a good bibliography is appended to each chapter, the illustrations are good, and present-day therapy is well described. This is a welcome book.

Announcement

April 15, 1965, is the closing date for receipt of applications from candidates wishing to appear for the WRITTEN EXAMINATION of the SUB-BOARD OF PEDIATRIC CARDIOLOGY. The examination will be given June 4, 1965. Address: John McK. Mitchell, M.D., Executive Secretary, American Board of Pediatrics, Inc., 6 Cushman Rd., Rosemont, Pa. 19010.

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Editorial

Pulmonary surfactant

*Stuart Bondurant, M.D.**
Samuel T. Giammona, M.D.
Indianapolis, Ind.

Although the importance of surface forces in the lung was first recognized more than 30 years ago, the major advances in understanding the physiology, physical chemistry, and biochemistry of the surfactant have come within the past 10 years, and the application of these concepts and techniques to clinical medicine is just beginning. It is important to appreciate something of the potential and limitations of these concepts and techniques as a basis for designing and evaluating the clinical studies which are forthcoming.

At an interface, the attraction of surface molecules into the subsurface phase is incompletely counterbalanced by attraction from similar molecules above the surface. The effect is to minimize the number of molecules in the surface layer and thereby the size of the surface layer. The resulting surface tension is a force directed parallel to the surface or interface and is measured in dynes per centimeter of length of surface.[1]

Since the molecules on a surface are continually attracted into the subphase, an amount of energy equal to that of the attractive force is required to maintain the molecule on the surface. The total excess energy represented by a surface is equal to the product of the surface tension and the area of the surface. This surface free energy defines precisely the work needed to create a surface. The surface energy required to inflate an atelectatic lung is equal to the product of surface area to be created and the surface tension of the newly created surface.

The foregoing concepts led Von Neergaard[2] in 1929 to emphasize the importance of surface forces of the lung and to predict that the respiratory units would be lined with material with low surface tension. Subsequently, Mead, Whittenberger, and Radford[3] showed that the familiar hysteresis of pulmonary pressure-volume loops is not evident in saline-filled lungs which present no air-liquid surface and is therefore related to surface phenomenon.

Radford measured the transpulmonary pressure in air-filled and saline-filled lungs and reasoned that the difference is due to the surface free energy of the air-filled lung. He assumed that the respiratory units had a surface tension approximating

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*Address: Department of Medicine, Indiana University Medical Center, 1100 West M[illegible], Indianapolis, Ind. 46[illegible]

that of serum (45 dynes per centimeter) and calculated the pulmonary surface area from the following relationship

$$\text{Surface area} = \frac{\text{Surface free energy}}{\text{Surface tension}}$$

This calculation produced an estimate of pulmonary surface area which was considerably less than the estimates made from histologic investigations.[4]

Pattle[5] demonstrated very low surface tension in bubbles obtained from the sputum of patients and animals with pulmonary edema. He presented convincing evidence that the material responsible for the low surface tension is a monomolecular film which lines the respiratory unit. The material is principally a lipoprotein containing large amounts of lecithin.

In addition, Pattle described the effect of surface tension of the alveolar lining on the pressure gradient across the capillary wall. The higher the alveolar surface tension, the greater is the negative pressure between the alveolar surface and the capillary wall. Mead and Avery[6] have shown that increasing alveolar surface tension to that of serum would increase the transcapillary pressure gradient by approximately 20 mm. Hg.

Much of the important work in this country has been stimulated or done by Clements and his colleagues. Clements, Brown and Rudolph independently demonstrated a material in lung extracts with very low surface tension and pointed out that if this value is used in Radford's calculation of surface area, the result is in close agreement with histologic estimates.[7] By using a modified Wilhelmy balance for the measurement of surface tension, Clements and associates showed that the surface tension of this material decreased greatly when the surface area was reduced. This low surface compressibility is an important characteristic of pulmonary surfactant. Clements reasoned that if such a decrease in surface tension with decrease in surface area occurred in the lung, the small alveoli would have low surface tension and less propensity for complete collapse, whereas larger alveoli would have greater surface tension which would resist further enlargement. This effect would stabilize the alveoli and increase the range of alveolar sizes which could coexist in continuity.[8] Gruenwald and associates have shown that in infants stability of the lungs is related to the presence of extracts which manifest large changes in surface tension with change in surface area, and Giammona and co-workers have shown a similar relationship in the lungs of animals maintained for long periods on the pump oxygenator and after pulmonary artery ligation.[9,10]

Extracts obtained by various techniques have been analyzed by several observers. Pattle's observations have been described. Brown showed that the phospholipid extracts contain large amounts of dipalmitoyl lecithin, and Finley and co-workers have recently reported detailed studies of the lipid content of the extracts.[11,12] Synthetic lecithin closely reproduces some of the surface characteristics of the lung extract. However, the composition of the monomolecular film which forms after addition of lung extracts to a surface has not been established, since lung extract contains small quantities of several other lipids which are sufficient to form a surface film.

Klaus and associates[13] have presented evidence that the surfactant is synthetized in the mitochondria of alveolar septal cells.

In summary, there is good evidence that the respiratory units are lined with a monomolecular film of lipoprotein which is synthetized in the alveolar septal cells, that dipalmitoyl lecithin is a major constituent of the film, and that the low surface tension of the film reduces the energy required to open collapsed lung and decreases the pressure gradient across the wall of pulmonary capillaries. The characteristic marked decrease in surface tension with decrease in area of the surface (low compressibility) is an important factor acting to stabilize the alveoli.

Several important limitations must be considered before applying the foregoing concepts to clinical studies.

None of the techniques of extraction are highly specific for the alveolar lining. The possibility of factitiously concentrating an irrelevant substance must always be considered. Several biologic substances will produce low surface tension, and several techniques of extraction (mincing, foaming) are simply means of concentrating that

fraction of a mixture which has the lowest surface tension

The efficiency of the extraction procedure even in normal lungs is unknown. There is evidence that in unaerated lung extractability by the chopping technique is reduced.[14] It will be important in future clinical studies to demonstrate that observed differences in surfactant are not due solely to changes in extractability. Surface tension is in part determined by the ionic and protein content of the subsurface phase. These factors need to be controlled in the study of extracts from pathologic lungs.

Although the relationship between weight and surface area or weight and surfactant content appears to be reasonably constant in normal lungs, this relationship may be variable in diseased lungs. Therefore critical comparison of surfactant from normal and abnormal lungs will require measurements other than weight for assuring quantitative comparability of samples.

Altered surface characteristics of lung extracts have been described in several clinical conditions. Mead and Avery reported abnormally high surface tensions of extracts of lung of fetuses and of infants with hyaline membrane disease. They suggested that this disease, characterized by atelectasis, might be due in part to abnormality of surfactant. Gruenwald and co-workers showed that the lungs of infants with hyaline membrane disease had a low surfactant activity index and deficient stability. These meticulous studies have been confirmed in several laboratories and constitute strong evidence of altered surfactant in the lungs of infants with hyaline membrane disease.

Lung extracts with abnormally high surface tension have been described in the lungs of patients with atelectasis, pneumonia and after prolonged periods on cardiopulmonary bypass.[15,16] It would be important to relate these observations to the pressure-volume characteristics of the abnormal lungs.

Miller and Bondurant have shown that the application of tobacco smoke to aqueous surfaces and to lung extract causes profound changes in surface tension and similarly that the surface tension of extracts of lungs of animals exposed to cigarette smoke in life differs from that of normal animals. Cigarette smoke causes an increase in surface compressibility of the film, a change which would be expected to reduce the stability of alveoli.[17]

There has been little apparent effect of changing the surface tension of lung extracts by nebulizing detergents and other agents.[18] Since the normal alveolar lining has a surface tension lower than that of many of the agents used, these observations are expected. Interaction between the nebulum and the surfactant may occur, but it appears most likely that such interaction would produce a surface with increased surface tension.

There has been one preliminary report of the effect upon survival of nebulizing dipalmitoyl lecithin into infants with hyaline membrane disease.[19] The results of this study are inconclusive. Similar studies are now in progress in several centers.

Studies of the normal physiology and biochemistry of the surfactant will further define the composition, function and source of the material and will generate techniques of greater precision for extracting and measuring surfactant. The significance of surfactant in disease can then be more critically evaluated and rational therapeutic manipulation of surface forces designed.

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Clinical communications

New criteria for the electrocardiographic diagnosis of emphysema and cor pulmonale

Ronald H. Selvester, M.D.
*Herbert B. Rubin, M.D., F.A.C.P.**
Downey, Calif.

Pulmonary emphysema, a disease found most commonly among the male population over 50 years of age, is rapidly becoming a major health problem.[1] There is also an increased incidence of chronic heart disease among this same group. Frequently the electrocardiographic signs that have been described in emphysema are mimicked by acquired or congenital heart disease with right atrial enlargement, right ventricular enlargement, or right bundle branch block.[2] It has become increasingly important, therefore, to establish definitive electrocardiographic criteria which will identify right ventricular hypertrophy alone, emphysema alone, or the two in combination.

The electrocardiographic findings in right ventricular hypertrophy have been extensively studied by Sokolow and Lyon,[4] Roman, Walsh, and Massie, Myers, Klein, and Stofer,[8] and others. These changes consist of right axis deviation and anterior displacement of the mean QRS vector in the precordial leads. More recently it has been demonstrated in congenital and acquired heart disease that the so-called incomplete right bundle branch block pattern (rSr and rsR in Leads V and V3R) is not infrequently associated with mild or moderate right ventricular hypertrophy.[10]

Many investigators have reported on the electrocardiographic findings in pulmonary emphysema.[11,1] These changes are well defined by Zuckermann and his associates, who describe the vertical axis with increased voltage of the P wave, a prominent T wave, posterior and superior displacement of the QRS vector, and low voltage of QRS in both standard and limb leads. Although they give extensive descriptions of electrocardiographic patterns that reflect these changes, their descriptions are in general terms and do not give specific criteria for evaluating any given electrocardiogram. On the other hand, Spodick has elaborated specific electrocardiographic criteria (Appendix I) as being consistent with pulmonary emphysema.[3,4] His criteria, however, do not require low voltage or a posterior direction of the QRS vector.

In an evaluation of the electrocardiograms and vectorcardiograms of patients with congenital and acquired heart disease

From the Medical Science Service, R[illegible] Los Amigos Hospital, Downey, Calif., the Cardiopulmonary Laboratory [illegible] and the Chest Medicine Service, Los Angeles County Hospital, Los Angeles, Calif. Supported in part by the California Research and Medical Education Fund of the Tuberculosis and Health Association of California, the Los Angeles County Heart Association, and the Fresno County Heart Association.

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*[illegible] Professor of Medicine, Loma Linda University, Loma Linda, Calif. Address correspondence: Medical Science Service, Rancho Los Amigos Hospital, 7601 East Imperial Highway, Downey, Calif. 90[illegible].

**[illegible] Clinical Professor of Medicine, Loma Linda University, Loma Linda, Calif.; Assistant Clinical Professor of Medicine, University of Southern California, Los Angeles, Calif.

Table I. Spodick's ECG criteria applied to a selected series of subjects without emphysema

Series	Number in series	Positive for emphysema		Possible emphysema		No evidence of emphysema	
Normal	100	8	(8%)	12	(12%)	80	(80%)
Autopsies with no emphysema	183	32	(18%)	18	(10%)	133	(72%)
Congenital heart disease	256	92	(36%)	64	(25%)	100	(39%)
Total	539	132	(25%)	91	(17%)	313	(58%)

Table II. Spodick's ECG criteria applied to a series of 89 patients with pulmonary emphysema

Series	Number in series	Positive for emphysema		Possible emphysema		No evidence of emphysema	
Autopsies with emphysema	17	11	(65%)	3	(17.5%)	3	(17.5%)
Clinical emphysema	72	41	(57%)	16	(22%)	15	(21%)
Total	89	52	(59%)	19	(21%)	18	(20%)

Table III. The proposed ECG criteria applied to a series of 89 patients with pulmonary emphysema

Series	Number in series	Positive for emphysema		Possible emphysema		No evidence of emphysema	
Autopsies with emphysema	17	11	(65%)	1	(6%)	5	(29%)
Clinical emphysema	72	46	(64%)	10	(14%)	16	(22%)
Total	89	57	(64%)	11	(12%)	21	(24%)

in whom there was right atrial enlargement, right ventricular enlargement, or right bundle branch block. It occurred to us that many of these patients without any evidence of pulmonary disease might meet Spodick's criteria. A preliminary study was made in a selected group of patients with proved congenital heart disease (Table I, third line). It soon became apparent that by Spodick's criteria for pulmonary emphysema, more than one half of the patients with significant right atrial enlargement, right ventricular enlargement, and right bundle branch block had findings that were either consistent with or indicated possible emphysema.

Therefore, we decided to analyze a series of patients with emphysema, a series of patients with congenital heart disease, and a series of normal subjects in an attempt to develop criteria sufficiently refined to detect patients with pulmonary emphysema with and without right ventricular enlargement, and to distinguish these patients from those with the numerous other causes of right atrial enlargement, right ventricular enlargement, and right bundle branch block.

Materials

Seventy-two patients with emphysema were selected from the Chest Medical Service of the Los Angeles County General Hospital and the Cardiopulmonary Laboratories of the White Memorial Hospital

and Rancho Los Amigos Hospital. The presence of emphysema was determined by history, physical examination, chest x-ray films, and pulmonary function tests, which included vital capacity, residual volume (helium washout), and maximum breathing capacity. The severity of clinical emphysema was graded on a scale of 1-4 based on subjective dyspnea and physical findings as follows: *Grade 1*: Slight limitation with extensive exertion, and a slightly prolonged expiratory phase on physical examination. *Grade 2*: Dyspnea on climbing two flights of stairs or with running, and a mild to moderate increase in expiratory phase. *Grade 3*: Dyspnea on climbing one flight of stairs or walking one block on the level, and moderate increase in expiratory phase. *Grade 4*: Dyspnea on walking on level, inability to climb stairs, and a marked increase in expiratory phase.

Chest films were graded on a scale of 1-4 as follows: *Grade 1*: Minimally increased radiolucency, minimal flattening of the diaphragms with a normal or only minimally elongated cardiac shadow. *Grade 2*: Moderately increased radiolucency, moderate flattening of the diaphragms and elongation of the cardiac shadow, and minimal widening of the intercostal spaces. *Grade 3*: Markedly increased radiolucency, diaphragms flattened with only a minimal downward curving laterally, long narrow cardiac shadow, and moderate widening of the intercostal spaces. *Grade 4*: Marked radiolucency, elongation of the heart shadow, flat diaphragms often with fasciculation and lateral upward curving, and marked widening of the intercostal spaces.

Our pulmonary function grade was made up of the average grade for vital capacity, residual volume, and maximum breathing capacity. Vital capacity was graded on the following scale: Grade 1, 80 per cent of predicted; Grade 2, 60 per cent; Grade 3, 40 per cent; Grade 4, 20 per cent. Residual volume was graded on the following scale: Grade 1, 180 per cent of predicted; Grade 2, 250 per cent; Grade 3, 320 per cent; Grade 4, 400 per cent. Maximum

Table IV. Proposed ECG criteria in relation to right ventricular hypertrophy in 89 patients with pulmonary emphysema

Diagnosed by proposed criteria	Evidence in favor of right ventricular hypertrophy: S_1, S_2, S_3 or $S_1 Q_3$ patterns in Lead 1	Evidence in favor of right ventricular hypertrophy: Met Sokolow and Lyon's criteria	No evidence of RVH	Total
Positive or possible emphysema	28	7	33	68
No emphysema	8	1	12	21
Total	36	8	45	89

Table V. Proposed ECG criteria applied to 539 selected subjects without emphysema

Series	Number in series	Positive for emphysema		Possible emphysema		No evidence of emphysema	
Normal	100	2	(2%)	2	(2%)	96	(96%)
Autopsies with no emphysema	183	5	(3%)	5	(3%)	173	(94%)
Congenital heart disease	256	4	(1.5%)	12	(4.5%)	240	(94%)
Total	539	11	(2%)	19	(3.5%)	509	(94.5%)

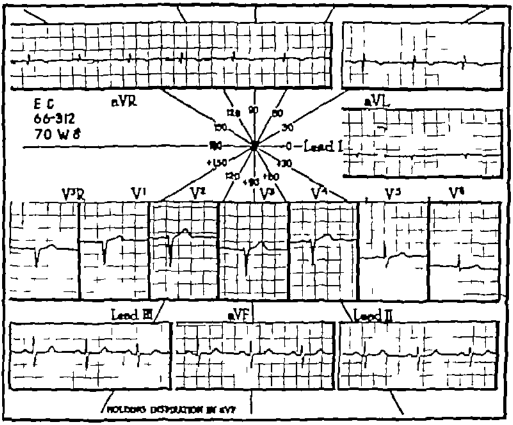


Fig. 1 Typical tracing from a 70 year old man with clinical x ray and pulmonary function evidence of advanced pulmonary emphysema and no evidence of right ventricular hypertrophy or right heart failure Note the specific changes of emphysema (1) The verticalization of the P wave axis to +90 degrees with normal voltage of the P waves (2) Maximum QRS voltage of less than 0 mm in the limb leads and Lead V (3) A QRS axis that is indeterminate in limb lead and −60 degrees chest leads with the transition zone between lead V and V (the mean QRS is superiorly and posteriorly displaced from its normal location)

breathing capacity was graded on the following scale Grade 1 76 per cent of predicted Grade 2 53 per cent Grade 3 30 per cent Grade 4 10 per cent

Total clinical grade was an average of three values (1) the clinical grade (2) the x ray grade and (3) the average pulmonary function grade Only those with a total clinical grade of greater than 1 were included in the series 24 patients had a total clinical grade of 1 1 to 2 and hence had only mild pulmonary emphysema by these criteria the other 48 patients had a total clinical grade of 2 1 to 4 and therefore had moderately severe to severe pulmonary emphysema by these criteria

An additional 17 cases in which there were definite autopsy findings of diffuse emphysema were included This gave us a total of 89 patients with either clinical evidence or autopsy proof of emphysema Six patients who otherwise met the above mentioned criteria were not included because of atrial arrhythmias

Two hundred fifty six patients with congenital heart disease were selected from the Cardiopulmonary Laboratories of the White Memorial Hospital and Rancho Los Amigos Hospital because of lesions known to be associated with a high incidence of right atrial enlargement right ventricular enlargement and right bundle branch block This group consisted of 95 consecutive cases of secundum type of atrial septal defects 11 cases of primum atrial septal defects 41 cases of pulmonary stenosis with intact septum 39 cases of pulmonary stenosis with left to right

shunts 35 cases of ventricular septal defects 20 cases of tetralogy of Fallot and 12 cases of transposition of the great vessels or persistent truncus arteriosus Diagnosis was established by cardiac catheterization and/or angiocardiography in all All consecutive patients available in each category were used without further selection These patients had no evidence of emphysema or diffuse pulmonary disease by history or physical or x ray examination All had pulmonary function tests which showed no evidence of emphysema or other obstructive pulmonary disease except for patients under the age of 10 who were deemed to be too young to cooperate Emphysema in this group is rare

One hundred normal subjects including student nurses graduate nurses house staff officers and medical students from the White Memorial Hospital were used as controls Each had a negative history and physical examination and a normal chest x ray film and electrocardiogram

The records of 200 consecutive patients from the White Memorial Hospital who came to autopsy and had electrocardiograms with sinus rhythm were studied retrospectively to further validate the criteria The 17 cases with definite pathologic evidence of emphysema mentioned above were found in this series Thirty nine patients were not included in this series because of electrocardiograms with atrial arrhythmias or complete heart block One of these had pulmonary emphysema

Methods and results

Standard 12 lead or 13 lead electrocardiograms were examined for each patient and control subject Only those tracings with sinus rhythm were subjected to analysis since a normally conducted P wave is essential in the criteria used We subjected the series of patients with emphysema to Spodick's criteria and found that the criteria were about as sensitive in this series as reported (Table II) [3,4] We then subjected the series of patients with congenital heart disease to the same criteria and found that the majority of the patients with right ventricular hypertrophy right atrial enlargement or right bundle branch block also met these criteria (Table I) In reviewing the data to see why Spodick's criteria had failed to separate the two groups we observed that most of the subjects with pulmonary emphysema had posteriorly and superiorly displaced QRS vectors whereas those with congenital heart disease and right ventricular hypertrophy had anteriorly right

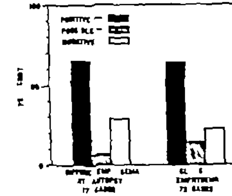


Fig 2 The proposed criteria for the electrocardiographic diagnosis of pulmonary emphysema as applied to the 89 cases of autopsy proved or clinically demonstrable emphysema There is no statistically significant difference in the performance of these criteria in either group

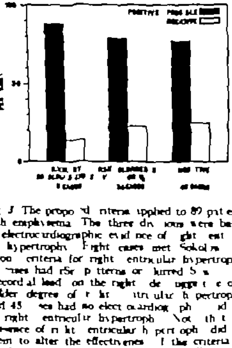


Fig 3 The proposed criteria applied to 89 patients with emphysema The three divisions were based on electrocardiographic evidence of right ventricular hypertrophy Eight cases met Sokolow and Lyon criteria for right ventricular hypertrophy 36 cases had rSr' patterns or slurred S waves in precordial leads on the right side suggestive of milder degree of right ventricular hypertrophy and 45 cases had no electrocardiographic evidence of right ventricular hypertrophy Note that the presence of right ventricular hypertrophy did not seem to alter the effectiveness of the criteria for emphysema since there is no statistically significant difference between these groups

wardly and slightly inferiorly displaced late QRS vectors. Also voltage in most of the patients with emphysema was found to be 0.7 mv. or less in limb leads and Lead V_6 whereas all but a very small percentage of the patients with congenital heart disease had voltages greater than this. The P axis in the limb leads was greater than +60 degrees in all but a small percentage of the group with emphysema and in most of the group with congenital heart disease, thus failing to separate these two groups from each other but separating them from normal subjects and from those with other types of heart disease. In a review of the data from the 100 normal subjects, it was noted that all but 2 had voltages greater than 0.7 mv. in limb leads and Lead V_6. These observations led us to the following criteria.

Proposed criteria

CONSISTENT WITH PULMONARY EMPHYSEMA (Fig. 1). P wave axis in the limb leads (frontal plane) greater than +60 degrees* (P more negative than positive in Lead aV_L and low or flat in Lead I) and one of the following: (A) Low voltage of the QRS (0.7 mv.) in the limb leads *and* in Lead V_6; (B) Posterior and superior displacement of the mean QRS axis, that is, mean QRS axis in the precordial leads of −30 degrees† or beyond and in the limb lead QRS axis of +70 degrees or more, indeterminate axis, or left axis of −30 degrees or beyond.

POSSIBLE PULMONARY EMPHYSEMA. Frontal angle of P greater than +60 degrees and low voltage of the QRS (0.7 mv.) in either limb leads *or* Lead V_6, but not in both.

NO EVIDENCE OF PULMONARY EMPHYSEMA. All tracings that fail to meet the above-mentioned criteria or those that meet the above-mentioned criteria but show obvious evidence of myocardial infarction.

When the proposed criteria were applied to the electrocardiograms of the 89 patients with clinically demonstrable or autopsy-proved emphysema (Table III), 57 patients (64 per cent) met the criteria consistent with pulmonary emphysema, 11 patients (12 per cent) met the criteria of possible pulmonary emphysema, and 21 patients (24 per cent) failed to meet these criteria. These data are graphically summarized in Fig. 2.

Thirty-six of the patients with emphysema had slurred S waves or rSr′ patterns in precordial leads on the right side suggesting either early right ventricular hypertrophy or conduction defects of the right bundle branch but failed to meet Sokolow and Lyon's criteria for right ventricular hypertrophy (Table IV). Twenty-eight of these 36 patients met the criteria proposed for emphysema; 8 failed to meet the criteria. An additional 8 patients with emphysema had an anterior displacement of the QRS loop with predominant R waves or rsR in right precordial leads and hence met modified Sokolow and Lyon's criteria in Lead V_1 for right ventricular hypertrophy.‡ In spite of this, the tracings in 7 of these 8 patients with presumed right ventricular hypertrophy were read as being consistent with pulmonary emphysema by the proposed criteria (Fig. 3). In 1 case the electrocardiogram was read as negative, but it exhibited unusually prominent and peaked P waves in Leads II, III, and aV_F and borderline voltage criteria, which strongly suggested emphysema as the underlying cause.

To evaluate the relationship between slurred S waves, rSr′ patterns, and predominant R waves in Lead V_1 and cor pulmonale, the cases of 3 patients who had undergone right heart catheterization and of 8 who had been autopsied were reviewed in the clinical series. An additional 11 patients without evidence of myocardial infarction were included from the autopsy series, bringing the total to 22 in both groups. Five had slurred S waves in precordial leads on the right side, 2 had rSr′ in these leads, and 2 had predominant R waves. All but one of these had right ventricular hypertrophy at autopsy or right ventricular systolic pressures over 40 mm. Hg at the time of right heart catheterization. Thirteen had none of these suggestive evidences of right ventricular hypertrophy.

*The [illegible] reference [illegible] represented by the axes of the bipolar (Einthoven) and unipolar (Wilson) [illegible] leads.

†Using the horizontal plane reference to [illegible] precordial [illegible] clockwise rotation with [illegible] Lead V_1 being equal to or greater than the R in Lead V_6.

‡The R/S or R/S ratio [illegible] Lead V_1 greater than 1 [illegible] R wave [illegible] Lead V_1 greater than 0.7 mv.

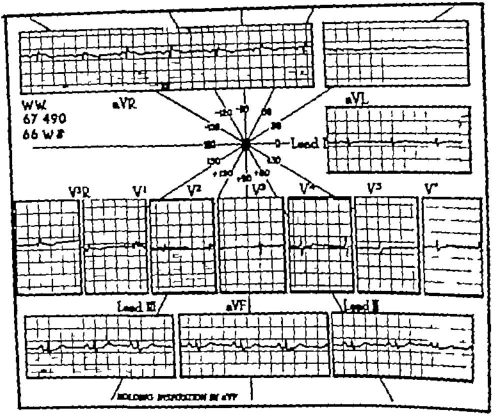


Fig 4 The tracing an example of pulmonary emphysema with a mod rate dy imposed right ventricular hypertrophy The electrocardiogram from a (6 y ar-ld r abundant clinical x ray and pulmonary function e idence of advanc l pulmo y sema He had also had one ep sode of right heart f lure Note the vertic lent n l (+80 degrees) with ome peak ng of the P wave in Limb Leads II III and V P wa es however m well below that usually associated w th P pulmonale Th R/ right precordial l ad greater than 1 and the voltage in limb lead and I m

in their electrocardiograms and all but 2 of these had normal right ventricles at autopsy or right ventricular systolic pressures under 30 mm Hg at the time of cardiac catheterization This is a highly significant correlation (p factor less than 0 01) Fig 4 is an example of a typical electrocardiogram of a patient with emphysema and presumed superimposed moderate right ventricular hypertrophy

In the series of 2.6 patients with congenital heart disease (Table V) the tracin in 4 patients (1 5 per cent) were read as being positive for emphysema those in 12 patients (4 5 per cent) as indicating possible emphysema and those in 240 patients (94 per cent) as being negative using these proposed criteria (Fig 5) In the normal series of 100 subjects (Table

V) the tracings w per cent possible tive in 96 per cent (

These criteria t in the diagnosis of known pulmonary without cor pulmo discriminated bet normal subjects or heart disease with trophy right atrial bundle branch blo demonstrated tha could detect emp series of patients many of which electrocardiogra

Therefore spective study

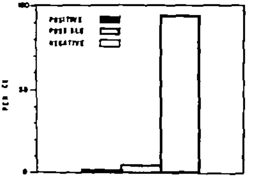


Fig. 5. The proposed criteria applied to 256 selected patients with congenital heart disease and lesions that commonly produce various degrees of right atrial enlargement, right ventricular hypertrophy, and right bundle branch block. None had evidence of pulmonary emphysema.

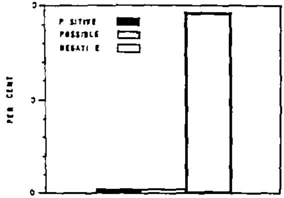


Fig. 6. The proposed criteria applied to 100 normal subjects.

an autopsy series of 200 consecutive patients who also had electrocardiograms with normal sinus rhythm. All tracings in this series were read by both of us without prior knowledge of the pathologic findings. The results of this study are shown in Fig. 7. Seventeen patients had definite evidence of pulmonary emphysema at autopsy (Table III). Eleven of these cases (65 per cent) were read as positive, one (6 per cent) as possible, and 5 (29 per cent) as negative. One hundred eighty-three patients had no significant emphysema at autopsy (Table V). 5 (3 per cent) of these cases were read as positive, 5 (3 per cent) as possible, and 173 (94 per cent) as negative by the proposed criteria.

Discussion

False positives (cases incorrectly diagnosed as consistent with pulmonary emphysema). The proposed criteria, which include the changes in voltage and the posterior and superior displacement of the mean QRS vector, as well as the P axis shift, eliminated all but 2 per cent of the false positives that had been found with Spodick's criteria.

The small per cent of false positives remaining met our criteria primarily because of the P wave changes and low voltage rather than because of the P wave changes and the QRS axis shifts. When we decreased the voltage criteria to 0.6 mv. or less in limb leads and Lead V_6, we eliminated all but 6 of the false positives in the 539 nonemphysematous subjects, an error of 1 per cent. However, this change decreased by 15 per cent the sensitivity in the group with emphysema. Thus, from these data it seems apparent that this degree of low voltage (0.6 mv. or less) associated with a posterior and superior mean QRS vector, a P axis greater than +60 degrees, and no electrocardiographic proof of myocardial infarction is almost pathognomonic of pulmonary emphysema.

The posterior and superior displacement of the QRS vector as well as the low voltage mentioned above can also occur in myocardial infarction.[8,11] Usually, this is associated with a normal or left axis of the P wave in limb leads. A significant number of cases, however, occurred with right axis shift of the P wave, and these

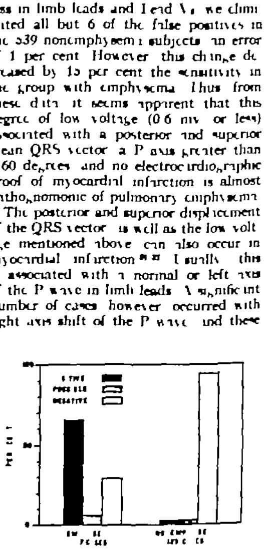


Fig. 7. The proposed criteria applied to 200 consecutive autopsied patients who also had electrocardiograms with sinus rhythm.

were indistinguishable from cases of emphysema with our criteria. For this reason when the electrocardiograms met conventional criteria for myocardial infarction they were read as negative even though they otherwise met our criteria for emphysema.

False negatives (cases of pulmonary emphysema that failed to meet the proposed criteria). Five patients met standard criteria for left ventricular hypertrophy or had borderline electrocardiographic findings and a long history of hypertension. Presumably left ventricular hypertrophy, which produces an increase in voltage and leftward displacement of the QRS vector, masked the electrocardiographic changes of emphysema in these patients.

Five patients had obvious electrocardiographic evidence of myocardial infarction and their tracings were therefore called negative by these criteria. Four of these patients otherwise met the proposed criteria for emphysema.

In 11 false negative cases there was clinical evidence of emphysema and no explanation for the failure to meet the criteria for emphysema. Eight of these patients had rSr' or slurred S waves in Lead V_1. One additional patient had definite right ventricular hypertrophy. The vector forces that occur in right ventricular hypertrophy[22] are opposite to those that result from pulmonary emphysema and could presumably mask the changes produced by emphysema. However, this did not affect the sensitivity of the proposed criteria (Table IV). The percentage of patients missed with these criteria was no greater in the presence of right ventricular hypertrophy or rSr' patterns in Lead V_1 than in the absence of those findings.

Emphysema and/or superimposed right ventricular hypertrophy. The electrocardiographic changes produced by pulmonary emphysema and by right ventricular hypertrophy may be confused. Emphysema produces a posterior and superior displacement of the QRS axis (clockwise rotation) in precordial leads and is often misdiagnosed as right ventricular hypertrophy. Right ventricular hypertrophy, on the other hand, produces anterior and rightward displacement of the middle and terminal QRS vectors,[23, 24] hence rSr', rSR', rsR', or rR' patterns in Lead V_1 and S waves in lateral precordial leads that are in general proportional to the severity of the right ventricular hypertrophy.[9, 10] It seems reasonable to predict that as right ventricular hypertrophy develops in the presence of emphysema, there should again be anterior displacement of the middle and late QRS vectors. As its earliest manifestation this would produce a slur in the upstroke of the S wave in right precordial leads, as observed by Mounsey, Ritzman, and Silverstone.[7] Somewhat more advanced right ventricular hypertrophy would produce rSr' in these leads, as observed by Armen, Kantor, and Weiser[1] and others, and severe right ventricular hypertrophy should produce predominant R waves in these same leads and fulfill Sokolow and Lyon's criteria.

In our hands the vectorcardiogram has been most useful in the detection of early right ventricular hypertrophy in patients with acquired and congenital heart disease. Right heart catheterizations are being performed on a group of patients with emphysema in order to secure objective evidence of right heart overload, and the findings are being correlated with the electrocardiographic and vectorcardiographic changes. From our studies to date it has been observed that emphysema of a severe degree may occur without pathologic or catheterization evidence of right heart overload. Therefore, the term cor pulmonale should not automatically be applied to patients with emphysema but rather to those with evidence of right ventricular hypertrophy resulting from emphysema or any other pulmonary disease.

Summary

1. Pulmonary emphysema produces verticalization of the P axis and a posterior and superior displacement of the mean QRS axis with decreased voltage. Right ventricular overload may also cause verticalization of the P axis, but on the other hand produces anterior and rightward displacement of the middle and terminal QRS forces that results in rSr' patterns or classic changes of right ventricular hypertrophy in precordial leads on the right side and right axis deviation in limb lead

2. Electrocardiographic criteria based on these changes are proposed to diagnose pulmonary emphysema with and without right ventricular hypertrophy and to distinguish such patients from those with right ventricular hypertrophy without emphysema.

3. The proposed criteria clearly separated patients with emphysema from normal subjects and from patients with congenital heart disease with right atrial enlargement, right ventricular hypertrophy, or right bundle branch block.

4. In the series studied these criteria proved to be as accurate in detecting pulmonary emphysema in the presence of right ventricular hypertrophy or conduction defects on the right side as in their absence.

5. Emphysema with superimposed right ventricular hypertrophy (cor pulmonale) is characterized by rsR' patterns in precordial leads on the right side or predominant R waves in these leads in addition to the changes of emphysema described in this report. It is probable that rSr' patterns or slurred S waves in precordial leads on the right side in these patients may also represent superimposed early right ventricular hypertrophy.

6. Myocardial infarction may mimic or mask the changes produced by emphysema, and emphysema alone may mimic myocardial infarction; hence the electrocardiographic diagnosis of emphysema is hazardous in the presence of electrocardiographic evidence of myocardial infarction.

7. In the absence of electrocardiographic evidence of myocardial infarction, definite low voltage (0.6 mv. or less in limb leads and Leads V_6) associated with a posteriorly and superiorly oriented QRS vector and an axis of the P wave greater than +60 degrees in limb leads is practically pathognomonic of emphysema.

8. This study has again emphasized the importance of distinguishing pulmonary emphysema alone from pulmonary emphysema with superimposed right ventricular hypertrophy. The term "cor pulmonale" should not be applied to emphysema but rather to right ventricular hypertrophy that results from emphysema or any other pulmonary disease.

Appendix I

Spodick's criteria for diagnosis of pulmonary emphysema[24]

POSITIVE DIAGNOSIS (CONSISTENT WITH DIFFUSE LUNG DISEASE). Any of the following were considered to be diagnostic regardless of other abnormalities on the tracings: (1) Presence of P pulmonale or unmistakable "Gothic" P in Leads II, III, and aV$_F$. (2) Frontal $\hat{A}$ P = +70 degrees or more and ±P waves to Lead V[illegible] or beyond, or precordial S wave of 2 mm. or more to Lead V_6 (or both). (3) Frontal $\hat{A}$ P = +60 degrees and all three of the following: Vertical or "axis illusion" $\hat{A}$ QRS, precordial S wave of 2 mm. or more to Lead V_6, and prominent ±P waves to or beyond Lead V_2.

POSSIBLE DIAGNOSIS. Any of the following were considered to be suggestive but not conclusive evidence of pulmonary disease: (1) Frontal $\hat{A}$ P = +60 degrees and any of the following: Vertical or "axis illusion" $\hat{A}$ QRS, precordial S wave of 2 mm. or more to Lead V_6, or prominent ±P waves to or beyond Lead V[illegible]. (2) Frontal $\hat{A}$ P = +30 degrees to +50 degrees and all three of the afore-mentioned factors. (3) Frontal $\hat{A}$ P = +70 degrees or more with frontal $\hat{A}$ QRS = +70 degrees or more.

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Closed chest cardiac resuscitation in patients with acute myocardial infarction

*Martin M. Nachlas, M.D.**
*David I. Miller, M.D.***
Baltimore, Md.

Reports of successful resuscitation after cardiac arrest secondary to acute myocardial infarction are beginning to appear in increasing numbers.[1-6] These rather sensational therapeutic accomplishments can be considered to be the direct result of the transfer to clinical medicine of three techniques long known to be effective in the laboratory, namely, mouth-to-mouth respiration, external cardiac massage, and external countershock. These important principles were first described in their respective order in the Bible,[7] by Boehm in 1878, and by Hooker, Kouwenhoven, and Langworthy[9] in 1933. But it was not until Jan. 6, 1960, that all three features were employed for the resuscitation of a 45-year-old man who had developed ventricular fibrillation several hours after an acute coronary artery occlusion.

Since that time, similar successes from other institutions[11-14] have verified the fact that effective therapeutic measures exist which can restore to health even those patients with acute myocardial infarction whose convalescence is complicated by the appearance of ventricular fibrillation. The frequency with which such success can be achieved is not known. Several recent reports[4,16,17] indicate that only between 5 and 15 per cent of these patients can be resuscitated completely. Although this small success rate does not seem to be impressive, nevertheless, these are patients who never would have survived this arrhythmia in previous years. Important questions which remain to be answered are (1) What differentiates the patients who survive from those who do not? (2) What is the likelihood of success when optimal conditions for resuscitation prevail? (3) What constitutes optimal conditions?

During the past 2 years we have had experience with 60 patients who sustained cardiac arrest during an acute myocardial infarction. Our over-all salvage, like the results referred to above, has been small. However, we have recorded a number of observations which add to the presently available knowledge concerning death that occurs during myocardial infarction and concerning some factors related to successful resuscitation.

From the Departments of Surgery and Medicine, the Sinai Hospital [illegible]
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Methods and materials

During the period from June 10 1961 to February 20 1963 attempts were made to resuscitate 60 patients who sustained cardiac arrest during the course of an acute myocardial infarction. These were patients who were admitted to the hospital because of their myocardial infarction and not those who developed this illness as a complication of some other presenting medical or surgical condition.

When a cardiac arrest occurred the telephone operator was notified and the information relayed by a special call via the paging system. This coded alarm brought to the area several members of the medical and surgical house staff an anesthetist a nurse with the emergency drug cart the nursing supervisor on the floor an orderly from Central Supply with an equipment cart and a representative from the maintenance department.

Technique of resuscitation. The house staff has been instructed to begin closed chest massage immediately and the nurse or other house officer is advised to perform artificial respiration. Oral airways or resuscitubes were readily available in all treatment areas so that mouth to mouth ventilation could be performed readily through the airway. As other personnel and equipment arrived electrodes were attached in order to obtain an electrocardiogram and a cut-down was placed in the ankle. When the automatic external massage pump[11] arrived from Central Supply it was quickly adjusted on the patient thereby freeing the house officer. By this time the anesthetist had usually taken over the management of ventilation either with bag to mask respiration or with the placement of a cuffed endotracheal tube and the use of the automatic respirator. The A C defibrillator (Kouwenhoven or Electrodyne model) was connected to the electrical source. If ventricular fibrillation was noted countershocking was begun usually by giving a single shock or a series of three shocks about 1 second apart. Low voltages were tried initially (350 to 450 volts) but if conversion did not occur the higher voltages were used (650 to 750 volts). Massage was continued until a peripheral pulse was felt. Sodium bicarbonate (44 5 mEq) was usually given intravenously and vasopressors were infused as required.

During the early months of our resuscitation program the ideal technique just described was not always achieved. Aside from many variations in the details of the resuscitation procedure from patient to patient there were frequent uncontrolled gross deviations from this planned schema. For example because some residents lacked confidence in the efficacy of mouth to mouth ventilation attempts were occasionally made to intubate the patient under adverse circumstances and by inexperienced personnel. The consequent delay in oxygenation of the blood being circulated by massage undoubtedly contributed to some of the failures. Another error which was eliminated with time was the attitude that the initial action should be directed toward the acquisition of an electrocardiogram which necessitated the expenditure of precious time that should have been devoted to ventilation and massage.

Nature of collection of data. In the majority of instances (43 cases) one or both of us participated in the attempt at resuscitation. When the emergency was over we began collecting the information concerning the preterminal and terminal events from the person who had recognized the arrest and from the house officers who arrived before we did. Additional data were obtained from the physicians caring for the patient and from the chart.

Results

General observations. The ages of our patients ranged from 37 to 83 years. Thirteen patients were under 50 years of age 26 were between 50 and 64 years and 21 were over 65 years. Thus two thirds of the patients were under 65 years of age 22 per cent were under 50. There were 38 more men than women in this series. The cardiac arrest occurred in 39 patients during their first myocardial infarction in 13 patients during a second infarction and in 8 patients who gave a history of two or more previous infarctions. The diagnosis of an acute myocardial infarction was made by history and physical examination alone in 9 patients whereas in 51 patients positive laboratory or postmortem findings confirmed the diagnosis. The suggestive

history and physical findings were supported by a positive electrocardiogram in 35 instances and by elevations in the serial transaminase determinations (SGOT) in 32 cases. In 20 cases the values were greater than 100 units. When these patients were considered with regard to age and the number of the infarct, it was found that nearly one half of the group (28) were under 65 years of age and convalescing from their first coronary occlusion. This point is emphasized because of our conviction that many of these individuals can be restored to good health.

In a previous paper[10] we pointed out that 74 per cent of patients who die during the course of an acute myocardial infarction experience the terminal event within the first 5 days of their hospitalization. In the present series the arrest occurred on the first or second day in 41 of the 60 patients and on the third to fifth days in 9 patients. Thus 83 per cent of the arrests occurred within the high risk period during which all patients should be monitored continuously. It is apparent that the location of the patient in the hospital at the time of arrest might influence the likelihood of a successful resuscitation since certain areas are better prepared with personnel and equipment to handle this type of emergency. From these two viewpoints our intensive care unit (I.C.U.) and emergency room (E.R.) are about equally rated although there is much more work space in the I.C.U. The distribution of the sites where the arrests occurred was: 11 in the I.C.U., 30 in the E.R., and 19 in the private room areas. Because of the small number of successes, we were not able to find significant differences when comparing the results obtained in the three areas. Another matter of interest concerns the individual who gives the alarm. In 34 instances this was done by a house officer, in 16 cases by a nurse, and on 10 occasions by some other person such as family, orderly, or the patient himself. The likelihood of restoring these 26 patients who sustained cardiac arrest in the absence of a physician was diminished because of the inevitable period of delay in obtaining the house staff required for the institution of resuscitative measures. More recently, nursing personnel have been instructed in the techniques of mouth to mouth respiration and closed chest massage so that in a few instances resuscitation was started before the house physicians appeared.

Characteristics of the preterminal period. The recognition that death is impending would be of assistance in either preventing, if possible, or preparing for the cardiac arrest. Frequently, this event occurs without warning in patients who appear to be convalescing satisfactorily. However, in retrospect it becomes evident that in some patients who were thought to be doing well premonitory signs were indeed present. We have re-examined the 24 hour period preceding each cardiac arrest in order to determine the frequency of such warning signals.

One clinical finding which has been recognized as an event of serious consequence is the recurrence of chest pain after an asymptomatic interval. This occurred in 6 of our patients, in 3 of whom there were no other findings to make one suspect the impending cardiac arrest. Another foreboding observation is the presence of an arrhythmia. In 20 patients an electrocardiogram was not obtained during the preterminal period, either because the tracing taken earlier was thought to be adequate or because the arrest occurred so suddenly in the E.R. that time was not available. Forty patients had had an ECG taken within 24 hours of the arrest: 20 showed sinus rhythm and 20 had recognizable irregular cardiac action some time before arrest. There were 2 patients with supraventricular tachycardia, 15 with atrial or ventricular ectopic rhythms, and 3 with A-V block or dissociation. By emphasizing these findings we do not mean to imply that every patient with an acute coronary artery occlusion who shows some arrhythmia is likely to sustain cardiac arrest, but certainly these patients should be considered to be an increased risk group, and if the arrhythmia persists, the risk becomes even greater.

Digitalis and/or quinidine were used in the 17 patients whose arrhythmias were recognized at a time sufficiently early to permit their administration. The response to digitalis could not be evaluated because the drug was given too near the time of death. The value of quinidine in either

decreasing myocardial irritability so as to avert ventricular fibrillation or improving the ease of defibrillation is still unsettled.[9,28] Twelve patients received quinidine in adequate doses prior to cardiac arrest. In 6 ventricular fibrillation was recorded at the time of arrest. This is not significantly different from the incidence of ventricular fibrillation in our nonquinidinized patients. In this small number of patients the value of quinidine in aiding the return to a sinus rhythm or an adequate arterial pressure could not be judged. None of the 3 patients who were discharged in good condition had been given quinidine prior to arrest. Perhaps coincidentally, the 2 patients without ectopic ventricular beats after defibrillation had received quinidine.

Besides arrhythmias, evidence that the heart was failing in its hemodynamic functions would portend a grave outcome. Twenty-six of these patients became hypotensive sometime before the arrest. In 3 patients this occurred more than 24 hours earlier, in 10 it occurred from 1 to 24 hours, and in 11 the onset was less than 1 hour before arrest. Thus nearly one half of the patients gave ample warning so that the personnel and equipment necessary for resuscitation could have been mobilized.

The choice of vasopressor agents in treating cardiogenic hypotension is not derived from any particular rationale but usually reflects the personal preference of the attending physician. The three drugs used most commonly at our hospital are metaraminol (Aramine), norepinephrine (Levophed), and mephentermine sulfate (Wyamine). Of the 17 patients who were given Aramine, 8 had a good pressor response, but in 2 patients the effect was not sustained. Three patients had only a transient rise in pressure, and in 5 there was no effect whatsoever. One patient did not receive the drug for a long enough time to allow study of the response before cardiac arrest intervened. Eleven patients were treated with Levophed; in 4 it was given as the drug of choice, and in 7 it was used after the response to Aramine was noted to be ineffective. Arterial pressure was maintained near the normal range in 7 of these patients, whereas in 1 the effect was transient, and in 3 it could not be evaluated because the drug had been administered shortly before the terminal event. Wyamine was used in only 3 patients with 1 poor and 2 good responses. Although all of these patients eventually suffered cardiac arrest, observations made upon these 26 hypotensive patients pointed strongly to the superior qualities of Levophed.

Characteristics of the terminal rhythm. One of the interesting by-products of the recent experiences with resuscitation has been the knowledge gained concerning the terminal rhythm of patients who die suddenly during convalescence from their acute infarction. Previously, such information was sparse, since relatively few patients died at the time when an electrocardiogram was being recorded. In 1938 ventricular fibrillation was believed by many to be the main factor in the sudden death of those with severe heart disease. However, Greco and Schwartz predicted that when the evidence became available it would be found that just as many of these patients died in asystole as in ventricular fibrillation. This opinion was verified 10 years later in the classic paper of Stroud and Feil,[7] who recorded terminal electrocardiograms in 23 of their own patients and abstracted 57 additional cases from the literature. Indeed, only half of the patients who died suddenly showed ventricular fibrillation. Ten years after this study, Hellerstein and Turell[8] described the terminal electrocardiograms of 59 patients with coronary artery disease under their care. Surprisingly, they found ventricular standstill in 77 per cent of the cases and fibrillation in only 23 per cent.

For effective resuscitation, recognition of the terminal electrical complex is crucial. An electrocardiogram was obtained in 45 of these 60 patients either at the moment of death (6 cases) or within 4 minutes of this event. Twelve electrocardiograms were recorded from 5 to 9 minutes after the onset of clinical death, and three within 10 to 15 minutes. Three types of arrhythmias were observed: ventricular fibrillation was seen in 35 patients (58 per cent), ventricular standstill in 13 (22 per cent), and some other type of arrhythmia in 12 (20 per cent). The latter group of patients included those with chaotic patterns, atrioventricular dissociation, idioventr-

rhythm and atrioventricular block. Three patients still had favorable rhythms at the time of death: 1 had sinus rhythm, 1 had nodal rhythm, and 1 had supraventricular tachycardia. In the evaluation of the results we have combined these 12 cases with the asystole group, to which they seemed to be closely akin. The rhythm of 9 of these patients changed eventually to asystole.

We cannot state with certainty that some patients might not have had one type of rhythm at the time of clinical death and another when the ECG was taken a few minutes later. However, it would be most unusual in such a short time for an asystole to convert to fibrillation or for the reverse to occur. On the other hand, a change from asystole to some other type of rhythm might be noted when coronary circulation is restored by the institution of external cardiac massage. These matters are not of serious consequence since both of the latter groups of patients require the same treatment and do not need countershock. Our data are in fairly close agreement with those of Stroud and Feil in that slightly more than one half of the patients who died during acute infarction showed ventricular fibrillation as the terminal rhythm. We could not observe any relationship between the terminal rhythm and the age of the patient, the number of the infarct, or any features of the preterminal period.

Resuscitation features

ARTIFICIAL RESPIRATION. Theoretically, one of the most important factors influencing the likelihood of success is the time that elapses from the onset of the arrest to the institution of treatment. This is not always easy to determine since under stressful circumstances observations of time and order of events or procedures are often not recorded. We selected the 4 minute period as the upper limit of acceptable delay between the onset of arrest and the institution of treatment. This time is said to represent the upper limit of safety with regard to the reversibility of brain damage after cessation of circulation.[2,3] In 51 of the 60 patients adequate artificial respiration was begun before 4 minutes had elapsed; in 6 patients a longer time had passed, and in 3 the exact time was unknown. Mouth to mouth ventilation was the method used in 28 patients, whereas in 22 patients the trachea was intubated at the outset. Eight patients had oxygen delivered by face mask, and in 2 cases the technique used was not certain. No one would question the superiority of the technique by which oxygen is delivered to the trachea through a cuffed tube which can prevent regurgitation of intestinal contents. The serious deficiency associated with this procedure is the delay in instituting artificial respiration when the intubation is attempted by inexperienced personnel, when the intubation is difficult because of anatomic or mechanical features, or when there is insistence that other techniques are suboptimal and inefficient and must be abandoned as soon as intubation can be accomplished. Under these circumstances familiarity with the tracheal intubation procedure may do more harm than good. During this experience with resuscitation it has become apparent that mouth to mouth method of artificial respiration is highly effective and should be employed immediately and continuously until the anesthetist is ready with his equipment to change over quickly and smoothly to automatic ventilation through an endotracheal tube.

ARTIFICIAL CIRCULATION. In 58 of the 60 patients adequate massage was begun in less than 4 minutes after the onset of the arrest. Our definition of "adequate" is probably a little generous if evaluated by the standards that we use today. For example, this description was said to apply when a house officer appeared to be compressing the inferior portion of the patient's sternum with some vigor. A hard board was not placed under the back in all instances, the femoral pulses were not palpated routinely, and the effect of the massage on the size of the pupils was not noted regularly. These oversights were due in part to insufficient knowledge of the importance of the measures and in part to the need for action under urgent and excitable conditions. Our current view of adequate massage would envision a patient on the floor or with a bed board between his back and the mattress, a house officer kneeling over the patient on the floor or on the bed and compressing the

lower end of the sternum 40 to 60 times per minute and another person observing the femoral pulse and the size of the pupils. A palpable pulse and small pupils are usually indicative of adequate sustaining circulation.

MECHANIZED CARDIAC MASSAGE. At the onset of this study the automatic portable pneumatic pump was not available and when it appeared the usual resistance to new equipment was displayed by some of the more conservative members of the house staff. Therefore not many of these patients had the benefits of mechanized massage which include producing sternal compression at a regular rate with adjustable even force with a constant duration of systole and without physically taxing and exhausting the operator.[15, 8] The freedom afforded one of the professional personnel can always be used to advantage in the management of the resuscitative measures. These benefits have now become more generally recognized at our hospital so that more patients are treated with mechanized massage. In practically every instance the adequacy of the artificial circulation was demonstrated even after period of massage which were in some cases as long as 60 to 120 minutes.

DIAGNOSIS OF THE ARRHYTHMIA. Although some of the urgency is removed when adequate respiration and circulation are effected the ultimate treatment is closely related to the type of arrhythmia. In 41 of the 60 patients visualization of the electrical activity of the heart was made in less than 4 minutes. This finding in itself is not necessarily praiseworthy because in a significant number of cases the early diagnoses were obtained at the expense of the performance of adequate resuscitative measures. Likewise in the one third of the patients in whom an electrocardiogram was not recorded for more than 4 minutes after the onset of arrest such delay was not due always to more attention to the resuscitative measures but more often to the absence of an ECG machine, the presence of 60 cycle interference or other technical difficulties. Because of these variables no correlation could be noted between the acquisition of an early diagnosis and the extent of restoration.

VALUE OF SIZE OF PUPILS. Ordinarily after cessation of circulation the pupils dilate widely and no longer respond to light. This occurs within a minute or two but may be delayed significantly if the patients have been given morphine shortly before the arrest. The records of the size of the pupils at the onset of resuscitation indicated that they were small in 38 patients, moderately dilated in 7, and widely dilated in 13, and in 2 the size was unknown. Aside from the exception mentioned these findings would suggest that two thirds of the patients came under observation relatively early after the arrest. The pupils became small in 11 of the 20 patients with dilated pupils after the onset of cardiac massage. Although slow dilatation of the pupils during resuscitative therapy is an ominous sign this occurrence or even the finding of widely dilated pupils does not necessarily mean that irreversible brain damage has occurred. Attempts at resuscitation should not be abandoned because of the size of the pupils alone.

Evaluation of resuscitative measures. Among the several recent reports of resuscitation by closed chest massage[1, 16, 17] a variety of categories was selected to grade the results. These ranged from simple resumption of cardiac action to complete recovery and discharge from the hospital (Table I). It is readily apparent that the restoration of cardiac activity can be accomplished in a high percentage of patients (32 to 70 per cent) but that the number who survive is much smaller (5 to 15 per cent). These survivors represent salvage from a condition that formerly was uniformly fatal. Although the ultimate goal is survival of the patient this result often depends upon factors other than adequate resuscitative techniques. A badly diseased heart may respond satisfactorily to the resuscitation efforts but still may not be capable of prolonged function. Therefore in order to evaluate the measures employed for resuscitation the most reliable criterion would appear to be the extent to which the individual is returned to his pre-arrest status. This means the restoration of a conducted beat, the reappearance of adequate arterial pressure, and the return of consciousness. This type of result was obtained in 22 to 73 per cent of

Table I. Results of closed chest resuscitation in patients with acute myocardial infarction

Authors	Year	Number of cases	Cardiac action restored		Return to pre-arrest status		Survivors	
			Number	%	Number	%	Number	%
Jude, Kouwenhoven, and Knickerbocker*	1961	47	22	46	11	23	7	15
Shipman, McCrady, and Bradford	1962	15	—	—	—	73†	2	13
Klassen, Broadhurst, Peretz, and Johnson	1963	60	42	70	17	28	8	13
Himmelhoch, Dekker, Gazzaniga, and Like	1964	22	7	32	—	—	1	5
Nachlas and Miller	1964	60	23	38	13	22	3	5

*Th[illegible] probably high[illegible] this group because these authors [illegible] the return of spontaneous [illegible] [illegible] cardiac activity.

†Th[illegible] figure [illegible] in this category because [illegible] is included in the [illegible] [illegible] apparently [illegible] Since they related the results to the total number of cardiac arr[illegible] [illegible] the ventricular fibrillation associated with acute infarction they had [illegible]

the cases (Table I). We have analyzed our data in greater detail by evaluating separately the electrical and hemodynamic functions of the heart and the return of performance of the central nervous system (Table II).

The recovery of the electrical activity of the heart was divided into three categories, namely, (1) no conversion, (2) conversion and stability for more than 5 minutes, and (3) conducted beats lasting over 1 hour. The first group included those patients with ventricular fibrillation in whom either countershocking was unsuccessful or recurrent fibrillation was noted. Patients with asystole or bizarre complexes were also included here when treatment did not result in a persistent and improved complex. Obviously, the resuscitative measures were totally ineffective in this group. The second class included those patients whose hearts were returned to a conductive state which was consistent with survival but which was temporary. They showed a rhythm in which the pacemaker was in the atrium or atrioventricular node. The third category included patients who responded well to the resuscitative therapy.

As Table II illustrates, there were 13, 33, and 14 patients, respectively, in each group. No differences were noted in these results when the group with ventricular fibrillation was compared with the group with standstill. Twenty-six of the 47 patients who developed a conducted beat had a persistent sinus rhythm at some time during the resuscitation period. The hemodynamic properties of the heart were evaluated by noting the presence of a blood pressure above shock level which persisted longer than 5 minutes with or without the assistance of vasopressors. In 37 patients such an effective sustained blood pressure could not be obtained, whereas in the other 23 patients this was accomplished with the aid of vasopressor agents in 14 and without drugs in 9 patients. Finally, the patients demonstrated varying degrees of recovery of the central nervous system by the return of spontaneous respiration in 21 individuals, 13 of whom also regained consciousness (Table II).

There were 13 patients in whom the results were bad, i.e., there was no recovery of either electrical activity, arterial

pressures or function of the central nervous system At the other extreme there were 12 patients in whom a sinus rhythm effective blood pressure and conscious state were restored A comparison of various features of the cardiac arrests in these two groups revealed no significant differences in the categories of age infarct number site of arrest pre arrest status terminal rhythm or time of onset of the measures of pulmonary and cardiac resuscitation It should be recalled that the time of onset of the resuscitation treatment refers to a period greater or less than 4 minutes and does not differentiate those in whom treatment was begun immediately from those in whom it was started at 3 or 4 minutes A few differences were noted between the group with very good results and the group with very poor results In 92 per cent of the cases of failure cardiac arrest occurred during the first 5 days of hospitalization whereas among the cases of success cardiac arrest occurred early in 42 per cent and after the 5 day period in 58 per cent As might be expected among the successes 5 of 7 patients received three or less countershocks whereas among the failures only 1 of 9 patients received so few shocks Also restoration was accomplished within 30 minutes in all but 1 of the 12 patients in whom resuscitation was successful The duration of the efforts of resuscitation among the instances of failure ranged from 20 to 130 minutes with 9 of the 13 patients being treated for more than 1 hour Finally it was noted that pulmonary resuscitation was administered after endotracheal intubation in 6 of the 13 instances of failure but in only 2 of the 12 instances of success This does not signify that tracheal intubation is less effective than mouth to mouth or mouth to airway ventilation but suggests rather that the delay encountered by striving for the seemingly more efficient mode of delivering oxygen results in greater harm than good

Discussion

When cardiac arrest occurs during an operation and resuscitation is successful this result is accepted as a matter of course because the patient was known to have a good heart and anoxia and acidosis are blamed for the arrest When arrest occurs after acute myocardial infarction and resuscitation is not successful this outcome is also treated as an expected event because the patient obviously had a badly diseased heart The notion that the heart might have been restored if the proper resuscita

Table 11 Detailed analysis of the response to resuscitative measures

Category	Ventricular fibrillation		Asystole		Totals	
	Number	%	Number		Number	%
Electrical recovery						
No conversion	9	26	4	16	13	22
Stable for 5 min	17	48	16	64	33	55
Conducted beat > 1 hr	9	26	5	20	14	23
Blood pressure						
None	20	57	17	68	3	62
With vasopressors	9	26	5	20	14	23
Unassisted	6	17	3	12	9	15
Central nervous system						
No recovery	22	63	17	68	39	65
Spontaneous respiration only	5	14	3	12	8	13
Conscious	8	23	5	20	13	22

*The patients with ventricular [illegible] type of arrhythmia [illegible] the group of patients with fibrillation.

tive measures had been employed is considered to be a remote possibility. In reviewing our experiences during the 20 month period covered by this report, we have accepted the working hypothesis that our failures were due in the main to inadequate resuscitative therapy. This may be an incorrect assumption, for it is equally possible that our failures were the result of attempting to resuscitate an organ which did not have the capacity for restoration. However, the latter view can be given serious consideration only when the therapeutic measures are known to be optimal. In many of our patients such circumstances obviously did not exist, whereas in others some features of the resuscitation may not have been performed properly without our realizing that such was the case. Many details in the resuscitative procedure were varied from one patient to another, and the exact influence of each variation is not known. We were able to record only the very gross deviations from what is theoretically considered to be good resuscitative technique. As time went on, many of the deficiencies in procedure were corrected and, consequently, the frequency of our successes did increase.[4]

The recognized errors which accompanied many of our attempts to resuscitate these 60 patients were related to the personnel involved and the technique used. New therapeutic teams often include some individuals with opposite notions about the correct procedure, others who have read uncritically some article about procedure or the value of a particular drug, and still others who happen to be on hand but lack enthusiasm for participation in what they consider to be a rather fruitless undertaking. Individuals of so varied orientation may make for an interesting discussion group but can hardly be expected to function smoothly in a therapeutic crisis which requires collaborative effort. We overcame this obstacle gradually by holding several teaching sessions for the house staff and by assigning the ultimate responsibility to the most senior medical and surgical persons present at the resuscitation.

Errors in techniques begin with the delay involved in starting treatment. Such delay developed because many patients were not being closely watched when the arrest occurred, and a variable amount of time was lost in recognizing the arrest and procuring the necessary professional personnel and equipment. Occasionally, concern with the application of electrodes for ECG recording and diagnosis was responsible for some loss of time. This problem has been handled by more active monitoring with electronic equipment and by attempting to place all high risk patients in the coronary care unit. Delay in starting artificial respiration was encountered too frequently, usually because the house officers, unconvinced of the efficacy of mouth to mouth ventilation, waited for the anesthetist to pass an endotracheal tube. Some were displeased with the technique for esthetic reasons, especially if the patient had vomited recently. Lack of a good suction apparatus occasionally made effective pulmonary ventilation impossible.

Inadequate circulation was believed to have obtained in some cases because of the failure to place a hard board between the patient's back and the mattress, because the massager remained standing and was at a mechanical disadvantage, and because the compression was not done with sufficient vigor. This last mistake resulted either from fatigue of the individual who performed the massage or from his purposely withholding effective force in order to avoid the complication of rib fractures. Another feature of the resuscitation that often leads to deficient artificial circulation is the strong desire of most medical house officers to observe the electrocardiogram while they are instituting cardiac massage. They will lean over to look at the tracing or even stop massage if the mechanical stimulation and motion produces electrical interference or artifact. Finally, suboptimal circulation has been obtained in some patients because of the insistence by the attending anesthetist that massage be suspended after every 3 or 4 compressions in order to allow unimpeded insufflation of the lungs. Such interruptions are undesirable and unnecessary, since there is sufficient time to ventilate effectively between compressions when they are performed at a rate of 40 to 50 times per minute.

Mistakes that were made with respect to the technique of defibrillation included

those of not applying the electrodes firmly to the chest wall, of giving currents that were too small (either 350 or 450 volts), and of not taking advantage of the added value of multiple shocks, usually three, given 1 second apart.[3] These deficiencies were eventually eliminated as familiarity with the defibrillator increased and as the staff began to accept the fact that in some individuals the current derived from a 450 volt shock was insufficient for defibrillation.

The errors concerned with the administration of drugs arose because of the hesitancy of some individuals to use epinephrine to stimulate heart action and because of frequent delays in getting the drugs into the proper syringe with the right sized needle and in the correct dosage. This last statement may sound absurd to anyone who has not been present at one of these crises. It should be remembered that physicians often request different drugs and different dosages under what seem to be similar therapeutic circumstances. Furthermore, many of these drugs are used infrequently, so that their procurement involves some searching through a drug cart or tray which has not been examined for a matter of days or even weeks. Drugs should be given by routes that ensure getting them into the circulation quickly enough and in adequate amounts. When intravenous solutions of norepinephrine are being injected, a check should be made to be sure that the needle did not become dislodged from the vein when the patient was shocked. Finally, when the crisis is over and the patient has a favorable electrocardiogram and a measurable blood pressure, it is still unwise to feel secure about the outcome. A physician should remain with the patient whose rhythm might still be variable, whose blood pressure is often unstable even with vasopressor agents, and who usually is still unconscious and receiving assisted respiration.

Summary

An experience with 60 patients who sustained cardiac arrest while convalescing from acute myocardial infarction has been described. Nearly one half of these patients were under 65 years of age and recovering from their first coronary artery occlusion. Eighty three per cent of the patients sustained their arrest within the first 5 days of hospitalization. In 38 of the 60 patients some warning of the impending event occurred in the form of recurrent chest pain, cardiac arrhythmias, or hypotension, whereas in 22 patients no premonitory symptoms or signs were noted. The cardiac arrests presented as ventricular fibrillation in 58 per cent, ventricular standstill in 22 per cent, and some other arrhythmia in 20 per cent. Although cardiac action was restored in 47 patients, 26 of whom had sinus rhythm, only 13 patients were restored to their pre-arrest status and only 5 were discharged from the hospital.

From observations made during these attempts at resuscitation, several conclusions appear justified. (1) All patients with acute myocardial infarction should be placed in a coronary-care unit with continuous electronic monitoring for at least 5 days. (2) When cardiac arrest is recognized, immediate attention should be given to the artificial circulation. External cardiac massage should be performed continuously and with sufficient vigor by a house officer or nurse until the automatic pneumatic pump can be substituted. A rate of 40 compressions per minute is desirable and should not be interrupted. (3) As soon as the artificial circulation has been instituted, mouth to mouth or mouth to airway ventilation should be started. Insufflation of the lungs can be achieved by this method between every other sternal compression. The change-over to endotracheal intubation and automatic respiration should be undertaken only when fully equipped and trained personnel are present. (4) Concern with the electrical characteristics of the arrhythmia should be demonstrated only at this point. Ventricular fibrillation is best treated by three countershocks given at 1 second intervals. If the current derived from the lower voltage (350 or 450 volts) is not effective, no hesitancy should be displayed in switching to shocks of 750 volts. Ventricular standstill or other types of arrhythmia which do not yield an effective arterial pressure should be treated with intracardiac epinephrine.

The standardization of the re-

tive measures had been employed is considered to be a remote possibility. In reviewing our experiences during the 20 month period covered by this report, we have accepted the working hypothesis that our failures were due in the main to inadequate resuscitative therapy. This may be an incorrect assumption, for it is equally possible that our failures were the result of attempting to resuscitate an organ which did not have the capacity for restoration. However, the latter view can be given serious consideration only when the therapeutic measures are known to be optimal. In many of our patients such circumstances obviously did not exist, whereas in others, some features of the resuscitation may not have been performed properly without our realizing that such was the case. Many details in the resuscitative procedure were varied from one patient to another, and the exact influence of each variation is not known. We were able to record only the very gross deviations from what is theoretically considered to be good resuscitative technique. As time went on, many of the deficiencies in procedure were corrected and consequently the frequency of our successes did increase.[4]

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Mistakes that were made with respect to the technique of defibrillation included

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Treatment of asystole or heart block during acute myocardial infarction with electrode catheter pacing

*R. A. Bruce, M.D.**
J. R. Blackmon, M.D.
L. A. Cobb, M.D.
H. T. Dodge, M.D.
Seattle, Wash.

Either transient asystole or complete heart block complicating acute myocardial infarction may cause syncope or Adams-Stokes attacks. Although complete A-V block occurs in less than 5 per cent of the patients with acute infarction, Courter, Moffat, and Fowler[1] reported that the mortality ranged from 39 to 100 per cent. Gale and Enfrox treated asystole with isoproterenol, and Vogel[2] used it to convert complete heart block. Nevertheless, myocardial oxygen consumption is increased by this catecholamine, and limited experience with its use in circulatory collapse associated with myocardial infarction revealed sudden death within hours.[3] Furman and Robinson[4] introduced the intravenous catheter pacemaker for the treatment of patients with complete heart block, whereas Parsonnet and associates found that a bipolar electrode required only 1 to 3 milliamperes of current. Samet, Jacobs, and Bernstein[5] reported dramatic benefits in 4 patients with *acute myocardial infarction* who were treated with a catheter pacemaker. All were promptly improved, and conversion to normal sinus rhythm resulted in 2. One died presumably from recurrent infarction, and another died from intracranial hemorrhage associated with anticoagulation therapy. Three other groups reported that the initial results of catheter pacing were satisfactory, but 3 out of 4 patients subsequently died from cardiogenic shock or other causes.[6-11]

Despite reported benefits of drug or pacemaker treatment of complete heart block complicating acute myocardial infarction, Courter, Moffat, and Fowler[1] concluded from a review of 18 cases that neither is required. Duration of block varied from 1 hour to 6 days, and no survivor had any block at the time of discharge. Nevertheless, 6 of these patients (39 per cent) died within 2 hours to 34 days, and 6 out of 9 with shock died. Autopsy revealed a recent thrombus in the proximal right coronary artery in 3 patients with fresh infarcts; another, who died after 21 hours, showed coronary sclerosis but no myocardial infarction.

Since the most desirable method for treating these patients is controversial, further observations on additional patients are timely, especially when immediate benefits occur along with hitherto unreported problems during recovery (Table I).

From the Department of Medicine, University of Washington, Seattle, Wash. 98105.
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*Address: Division of Cardiology, Department of Medicine, University of Washington, Seattle, Wash. 98105.

Patient 1 R.H.W. (UH 15020) was a 53 year-old white male physician who had been in excellent health prior to sudden onset of an acute postero-diaphragmatic myocardial infarction with complete heart block but normal duration of the QRS complexes. On admission to the hospital 30 hours after the onset, the blood pressure was 110/64 mm. Hg, the apical heart rate was 52 per minute with a regular rhythm. The heart was not enlarged, yet there was an obvious systolic bulge of the precordial impulse in the fourth intercostal space and the heart sounds were muffled. Serum glutamic oxalacetic transaminase activity rose to 570 units per milliliter and the erythrocyte sedimentation rate increased from 8 to 57 mm. per hour. Hypotension was treated with intravenous metaraminol. Electrocardiographic monitoring revealed varying myocardial ischemia. The heart rate accelerated from 52 to 64 beats per minute with atropine. Because premature ventricular systoles, cardiac dilatation, pulmonary congestion, and systemic venous hypertension developed on the third day, he was digitalized. Paroxysmal atrial fibrillation occurred transiently. Recurrent Adams-Stokes attacks due to asystole reached a crescendo during the fifth night (Fig. 1). Some attacks lasted as long as 17 seconds (Fig. 2) and were accompanied by convulsions. Between attacks the heart rate averaged about 74 per minute. A bipolar catheter electrode was inserted under local anesthesia into the right external jugular vein and passed into the outflow tract of the right ventricle. Five more asystolic attacks occurred during this procedure

Table I. Summary of clinical experiences

Patient	Age Sex	Myocardial infarction (number and location)	Indication for pacemaker catheter	Problem with insertion	Duration (days)	Complication on discontinuing pacemaking	Final rhythm and status
1 R.H.W. (#15020)	53 M	1 Inferior	35 Adams-Stokes attacks due to asystole, congestive heart failure	5 more attacks, nonresponsive areas in RV	5	Hypotension, inadequate cerebral function	NSR. Returned to work
2 D.C.M. (#41458)	61 M	4 Inferior	Adams-Stokes attacks, heart rate 36	Nonresponsive areas in RV	3	1° A-V block	NSR. Returned to work
3 E.D. (#4416[illegible])	30 M	2 Inferior	Syncope, marked bradycardia, nodal tachycardia after atropine	Ventricular fibrillation for 90 sec.	4	Return of A-V dissociation. Pulmonary infarction	NSR. Surviving
4 A.C. (#312950)	6? F	1 Inferior	First time: 2° A-V block. Second time: 3° A-V block. Congestive heart failure	Decrease in arterial pressure	6 6	Sudden block	NSR. 3° A-V block. Died
5 A.S. (#45a5[illegible])	?4 M	1 Inferior on seventh day	Syncope, ventricular asystole	None	4	Recurrences of A-V block on second day. Acute infarction	NSR. 1° A-V block
6 A.R.G. (#4635)	33 F	1 Not determined	Idioventricular rhythm. Syncope, shock, anuria from acute tubular necrosis	Interpolated ventricular beats unless pacemaker exceeded 100 per minute	39	Atrial flutter cardioverted to sinus rhythm with 2:1 conduction	Permanent pacemaker implanted. Improved
7 J.O. (#44811?)	46 M	1 Inferior	Hypotension, bradycardia. Changing A-V block. Early heart failure	None	3-1/3	None	NSR. Improved. Returned to work

Some ... of the right ventricular endocardium were not responsive to stimulation even though high voltage stimulus artefact was recorded from body surface electrodes. With effective pacing at 80 per minute there was an immediate clinical improvement in his sensorium and general status. Within 2 hours he discharged 1,050 ml of urine and exhibited an almost insatiable hunger for food. However the blood pressure had to be supported with metaraminol. Over the next 2 days the signs of congestive failure completely disappeared. Because of a further decrease in the intensity of the heart sounds together with a secondary rise in transaminase activity, it was postulated that the anterior wall of the heart probably had been contused during the resuscitative efforts for treatment of asystole.

By the ninth day occasional normal sinus beats with a first degree A-V block were interpolated with increasing frequency between pacemaker beats. A single run of sinus beats for 48 seconds occurred the next day. Attempts to reduce either rate or current of the pacemaker resulted in numerous interpolated beats, immediate hypotension and marked sweating. On the tenth day the pacemaker was discontinued with immediate restoration of normal sinus rhythm at a rate of 63 per minute. However the pacemaker had to be resumed $1\frac{1}{2}$ hour later because of the instability to maintain blood pressure even when the rate of intravenous infusion of metaraminol was greatly increased. The blood pressure promptly improved when pacemaker control was restored with a rate of 84 per minute. Later that day the pacemaker was discontinued again. After $8\frac{1}{4}$ hours he became weak ... while the spontaneous heart rate was ... to ... per minute and the blood pressure low. ... with the resumption of pacing again at a rate of 84 per minute the blood pressure stabilized at 116/... mm Hg and the mental status promptly returned to normal.

The pacemaker was permanently discontinued on the ... day and the electrode catheter was removed without incident the following day. He was started on a program of progressive activity beginning with ... on the fourteenth day of illness.

Comments. Atropine failed to prevent asystole and electrode catheter pacing should have been used earlier to prevent recurrent Adams-Stokes attacks. Further myocardial injury followed repeated asystole and external cardiac massage. Although circulation improved dramatically once pacemaking was instituted, it was of particular interest to observe subsequently the demonstration of acute circulatory insufficiency after the first few hours of spontaneous normal sinus rhythm. This was relieved promptly by resuming artificial pacing temporarily at a faster rate. Since stroke volume has been reported to be greatly reduced by infarction,[12] it is postulated that cardiac output was primarily dependent upon heart rate. After this transient period artificial pacing was not needed again and his subsequent convalescence was uneventful.

Patient 2. D. C. M. (UH 41458) was a 61-year-old white male maintenance engineer who was admitted to a local hospital with electrocardiographic evidence of acute posterodiaphragmatic myocardial infarction. He became hypotensive with atrial flutter and varying A-V conduction which changed to complete heart block. Although he was supported with oxygen, metaraminol and isoproterenol by intravenous infusion, Adams-Stokes attacks with convulsive seizures occurred repeatedly. He was transferred to the University Hospital on the 6th day. Examination revealed an acutely ill overweight man who complained of pain, shortness of breath and sweating. The blood pressure was 80/50 mm Hg, the apical heart rate was 26 per minute, and the respirations were 10 per minute. The heart sounds were quite faint and a ventricular gallop was audible. The jugular veins exhibited prominent A waves of rapid atrial contractions. Serum glutamic oxalacetic transaminase was 825 units per milliliter and blood urea nitrogen was 50 mg per cent. Within 2 hours a bipolar catheter electrode was inserted into the right ventricular outflow tract. With a rate of 85 per minute the blood pressure became normal, pain and dyspnea subsided and his sensorium immediately improved. Infusion of the pressor amines had to be stopped to avoid a hypertensive response. His subsequent course was completely uneventful and 3 days later the pacemaker was discontinued. Normal sinus rhythm with a rate of 65 to 75 per minute and first-degree A-V block occurred immediately. Two days later the catheter electrode was removed and he continued to do well.

Comments. This patient clearly demonstrated the failure of isoproterenol treatment and the value of prompt use of the electrode catheter. The uncomplicated course for the next few days contrasted with the numerous problems encountered in the first patient in whom this treatment was delayed for at least 24 hours. Constant monitoring with an oscilloscope failed to show any recurrence of arrhythmia.

Patient 3. T. D. (UH 4416...) was a 50-year-old white man who had had angina pectoris for several years and a previous myocardial infarction. On Dec 15, 1963 he developed severe chest pain which was followed by syncope. On admission to the hospital his systolic blood pressure was 0 mm Hg. He improved somewhat with oxygen, morphine and intravenous infusion of metaraminol, but the heart rate remained about 45 per minute because of sinus bradycardia with intermittent A-V block. The electrocardiogram showed a hyperacute posterodiaphragmatic infarction. He had a leukocytosis of 31,500

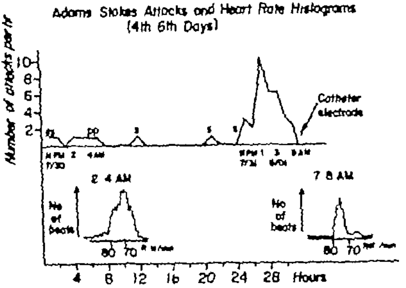


Fig. 3. Pattern of occurrence of Adams-Stokes attacks in Patient R.H.W. over a period of 30 hours. Histograms show heart rate at the times indicated. S represents spontaneous recovery, whereas P represents recovery by use of external pacemaker. On all other occasions recovery occurred with external massage.

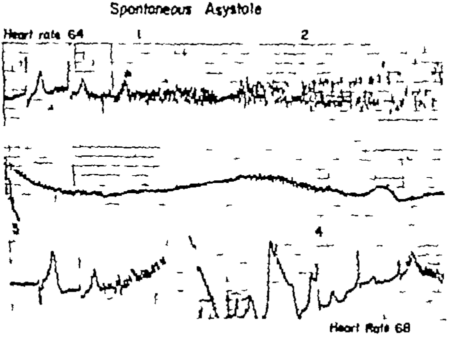


Fig. Example of asystole recorded in patient R.H.W. by portable tape recorder. Note ventricular escape and return of A-V nodal rhythm without QRS prolongation. There was no significant change in heart rate as a result of the asystole. *1* Onset of asystole for 17 seconds. *2* Skeletal muscle potential? *3* Ventricular escape. *4* Nodal rhythm.

Table II. Hemodynamic variations with various pacemaker sites in Patient N. C. (after spontaneous restoration of normal sinus rhythm on the sixth day)

Mechanism	Atrial rate	Ventricular rate	Stroke volume index (ml/M²)	Cardiac index (L/min/M²)	Mean arterial pressure (mm Hg)
Normal sinus rhythm 1° A V block	6	76	27	2 0	64
Pacemaker in right ventricular outflow tract	76	8	22	1 9	54
	76	91	20	1 8	52
Pacemaker in right atrium	85	85	27	2 3	66
	95	95	24	2 2	67

and the serum tr n m se ne t 132 units per milliliter whereas the erythrocyte sedimentation rate increased f m 3 to 3 ml per h ur After intravenous atropine for l ly ardia he developed nodal tachycardia and ventricular premature beats with a rate of 100 to 120 per minute. Since he developed a ventricular g ll p pulm n ry congestion and systemic enou hypertension he was digitalized. A bipolar catheter electrode was inserted into the right ventricle. During this procedure he developed ventricular fibrillation which persisted f 90 seconds until it was controlled by D C external defibrillation 1700 w tt sec nd. H te was maintained at 100 per minute, the blood pressure was supported with an infusion of metaraminol. After 2 days the pacemaker rate was lowered but the blood pressure fell but the electrocardiogram showed A V block. A similar response occurred when this maneuver was repeated on the fourth day. A treatment On the fifth day h we er the pacemaker was discontinued and he maintained normal sinus rhythm with a rate of 60 to 65 per minute. The catheter electrode was removed 4 days later.

Comments. This patient illustrates the necessity of being prepared to treat ventricular fibrillation when a catheter electrode is passed into the right ventricle. He also showed a transient period of unstable rhythm before normal sinus rhythm was restored permanently. During this interval the blood pressure and presumably the cardiac output varied with heart rate.

Patient 4. N C (KCH 3179 0) w 6 year-old hypertensive diabetic woman h had a myocardial infarction on Nov 25 1963. She was admitted to the hospital on the fourth day when she was found to have a slow heart rate. An electrocardiogram showed 2 1 A V block with a ventricular rate of 50. A catheter electrode was inserted into the right ventricle. On the sixth day she was found to have 1 1 A V conduction. Hemodynamic studies showed a fall in blood pressure stroke volume and cardiac output as compared with normal sinus rhythm when the heart was paced from the outflow tract of the right ventricle (Fig. 3, Table II). Since she developed a temperature of 101 F with chill the catheter was removed. The following morning she developed hypotension, bradycardia, clinical shock, and complete A V block. The pacemaker catheter was replaced in the right ventricle and it worked well. Nevertheless she developed left ventricular failure for which she was digitalized and diuresed. She continued to have persistent complete block whenever the pacemaker electrode was turned off during the next 5 days. She was clinically stable without pacer therapy until the thirteenth day when she died suddenly. Autopsy examination was not permitted.

Comments. This patient demonstrated that reversion to normal sinus rhythm for at least a day does not preclude the return of complete and persistent atrioventricular block. The importance of atrial systole for more effective stroke volume and arterial pressure as reported by Samet, Jacobs, Bernstein, and Shane,[?] as well as by Judge, Wilson, and Siegel,[12] was readily demonstrated. It appeared that she died of shock and heart failure but the relationship to the electrode catheter could not be determined. This emphasizes the possible hazard of dislocation of the catheter and the need for appropriate monitoring of such patients.

Patient 5. A S (I H 45557) was a 4 year-old retired white man who enjoyed good health until he experienced recurrent paroxysms of tachycardia. On admission Jan 29 1964 he suddenly felt faint and noticed dizziness and blurred vision every few seconds. He collapsed while standing. On examination he had second-degree A V block with a rate of 40 per minute. He was treated with isoproterenol aerosol. With this he felt faint from ventricular [illegible]

seconds (Fig. 4). He was treated with atropine which accelerated the sinus pacemaker but did not relieve the A-V heart block. On admission to the hospital he was alert and comfortable with a heart rate of 52 and blood pressure of 140/80 mm. Hg. The heart was not enlarged but the heart sounds were distant. The electrocardiogram showed complete A-V heart block with normal QRS interval but no recent myocardial infarction. He was monitored overnight and at 6 o'clock the next morning showed several episodes of ventricular standstill due to failure of A-V conduction. A bipolar catheter electrode was inserted into the outflow tract of the right ventricle. Pacemaker control was established promptly with a rate of 80 per minute. The patient remained asymptomatic and afebrile. On the third day the pacemaker was shut off and the patient immediately exhibited normal sinus rhythm with first-degree A-V block.

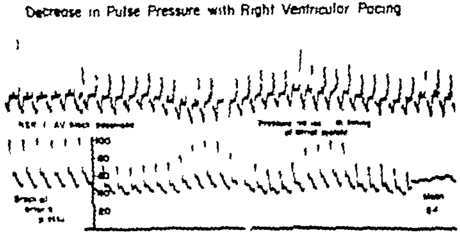


Fig. 3. Variations in arterial blood pressure during artificial ventricular pacing of Patient V. C. Note that pressure is lower except when the P-R interval happens to fall within normal range. The first 6 beats on the left were associated with higher arterial pressure when the rhythm was normal sinus prior to resumption of right ventricular pacing.

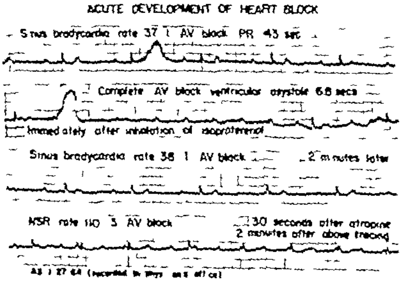
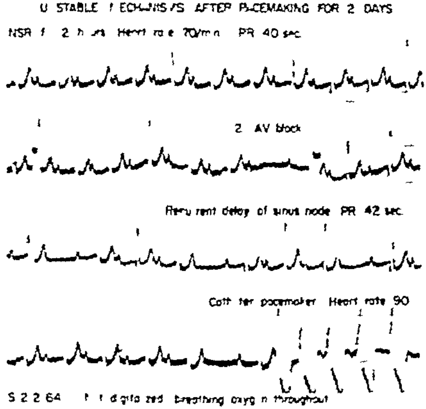


Fig. 4. Stokes-Adams ventricular standstill after inhalation of isoproterenol aerosol in Patient L. S. on second day of infarction. Note acceleration of sinus pacemaker especially after administration of atropine with appearance of third degree A-V block.



F t tent A V In tability of A V conduction 2 hours after resumption of sinus rhythm after 2 days of treatment with the catheter pacemaker. Final strip record prophylactic return to pacemaker control for period of hours during the night because she was not being monitored continuously.

Ex pt t e gle n nconducted beat this on t l t e hour before numer nonconducted beats were recorded (Fig. 5). The pacemaker resumed for several hours then discontinued without difficulty. As a safety measure over the weekend the pacemaker was used during the night hours. The subsequent course was uneventful until the seventh day when he felt tired and the ECG showed acute diaphragmatic infarction; the erythrocyte sedimentation rate subsequently rose to 69 mm. per hour.

Comment: This patient illustrates ischemia in the A V node manifested initially by paroxysms of tachycardia followed by Adams-Stokes attacks due to marked bradycardia from heart block and/or ventricular standstill. He responded very well to the use of the catheter pacemaker. After 2 days of pacing normal sinus rhythm was readily restored. Yet after 2 hours intermittent failure of the A V nodal conduction recurred. This was readily controlled by using the pacemaker again for a few hours.

Despite return of sinus rhythm with a marked first-degree A V block and while he was resting in bed he developed acute infarction on the seventh day.

Patient 6. A R G. (U.H. 4(35) 55-year-old woman developed syncope, hypotension and heart block with subsequent elevation of the transaminase level consistent with acute myocardial infarction. Since acute renal insufficiency from tubular necrosis occurred despite norepinephrine therapy for shock, she was transferred to the University Hospital for hemodialysis. Because of the precarious state of her circulation with idioventricular rhythm at 41 per minute a bipolar electrode catheter was placed in the right ventricle to improve cardiac output. In order to avoid interpolated sinus beats it was necessary to keep the pacemaker rate over 80 per minute. Examination of the heart revealed an ischemic systolic bulge over the precordium and an atrial gallop. The next day she developed acute pulmonary edema. Since she was still anuric hemodialysis was, except for 1 bed of 5 h, … fluid was removed with dramatic clinical improvement. Sixteen days after the pacemaker current had to be increased temporarily

to maintain control changing the battery power supply corrected this difficulty On the twenty first day atrial flutter occurred with a ventricular rate of 80 per minute when the pacemaker was shut off On the thirty eighth day cardioversion (100 watt seconds) restored sinus rhythm with 2 1 A V conduction Pacemaker electrodes were implanted surgically the next day but the postoperative course was complicated by hypotension hypovolemia and transient cerebral ischemia She improved and was discharged on the fifty third day when seen in the clinic 1 week later she was doing well except for occasional thoracic pain

Comments This case illustrates the recovery from acute tubular necrosis secondary to myocardial infarction complicated by hypotension and heart block in which artificial pacing played a major role Since normal sinus rhythm was not permanently restored a surgically implanted pacemaker was required Despite the several complications the eventual outcome justified the combination of procedures employed in therapy

Patient 7 J O (UH 48112) a 46 year-old white male dentist had severe chest pain radiating to the left shoulder on April 8 1964 with ECG evidence of acute posterodiaphragmatic infarction and elevation of the SGOT to 195 units per milliliter On April 13 the systolic blood pressure fell to 90 mm Hg as he developed a bradycardia with complete A V heart block On admission to the hospital he had second degree A V heart block with a rate of 45 per minute and a blood pressure of 95/60 mm Hg He exhibited ashen pallor and a prominent atrial gallop Pacing of the heart was instituted with a bipolar catheter electrode the blood pressure increased immediately to 120/78 mm Hg with a heart rate of 80 per minute Early signs of congestive failure disappeared On the second day of pacing interpolated sinus beats appeared and the pacing was discontinued after 3½ days of treatment Normal sinus rhythm appeared without any A V block and his subsequent course was uneventful

Comments This patient illustrates the prompt improvement in circulation and rapid return of normal sinus rhythm after the use of the electrode catheter pacemaker for second degree and third-degree A V block

Discussion

These 7 cases reveal both the benefits and the problems resulting from use of the catheter electrode for treatment of acute myocardial infarction complicated by complete heart block The 14 per cent mortality experience (1 death in 7 cases) was more favorable than the 62 per cent mortality experience represented by the 6 previously reported cases and was better than current experience reported by other cardiologists When compared with cases treated by conventional medical therapy [1] this mortality represents a substantial improvement although the case experience is rather limited

These studies point out the need to monitor patients with acute myocardial infarction more commonly if not indeed routinely for the first few days of illness This should be mandatory for patients with acute inferior or posterodiaphragmatic infarction The electrode catheter should be used as soon as Adams Stokes attacks syncope and/or A V dissociation appear The cardiologist should be prepared not only for adequate monitoring but also for external cardiac pacing and for treating ventricular fibrillation It is important to have a portable battery operated pacemaker available should it be necessary to move the patient to a different room for fluoroscopic guidance in placing the electrode catheter Certainly it is helpful to have an anesthesiologist in attendance although general anesthesia is neither necessary nor desirable The occurrence of convulsions and/or vomiting as a consequence of cardiac standstill during catheterization presents serious complications especially if a darkened room is used for fluoroscopy of the heart

Inasmuch as sinus rhythm returned in all but one of the patients one might assume that medical treatment with positive chronotropic agents such as atropine or isoproterenol would be preferable to using an internal pacemaker for a few days Nevertheless the experience recorded in this small number of patients clearly indicates the failures and hazards of such drug therapy The advantage of catheter electrode pacing is that the heart rate and cardiac output can be better controlled but myocardial metabolism is not increased beyond the requirements of a somewhat faster heart rate as it would be with isoproterenol [4]

The results obtained with catheter electrode pacing should encourage others to consider this treatment whenever syncope or Adams Stokes attacks from either asystole or complete heart block complicate acute myocardial infarction

Summary

1. Clinical experience with the use of a bipolar catheter electrode pacemaker is reported in 7 patients with acute myocardial infarction complicated by Adams-Stokes attacks due to asystole or complete heart block.

2. The use of a bipolar catheter electrode for 2 to 6 days resulted in spontaneous return of normal sinus rhythm in 6 patients, whereas another patient had a permanent pacemaker implanted surgically 6 weeks later.

3. Mortality was reduced to 14 per cent; the one fatality occurred in the single patient who was catheterized twice but who died unexpectedly on the thirteenth day. Survivors have returned to work after recovery from infarction.

4. Problems in management, especially with unstable cardiac mechanisms and conduction during a transition period in recovery, have been cited.

Appendix

Comparative clinical experience with cardiac pacing during acute myocardial infarction. In order to evaluate further the merits of electrode catheter pacing in patients with acute myocardial infarction and asystole or

Table III

	Illinois	*Seattle*	*Others*	*Altogether*
Number of patients	9	7	7	3
Ages				
Range (yr.)	57-81	46-73	53-83	46-83
Mean (yr.)	0	5	68	66
Men	5	5	3	13
Women	4	?	3	9
[illegible] infarction	4	4	3	11
Adams-Stokes attack	1	0	2	3
Type of [illegible] infarction				
Inferior or posterodiaphragmatic		6	1	14
Anteroseptal	[illegible]	0	4	6
Undefined, elevated SGOT	0	1	2	3
Indication for pacing				
Recurrent asystole	0	2	0	2
Marked bradycardia	1	2	0	3
[illegible] 3° A-V block	8	3	7	18
Complications of pacing				
None	8	0	4	13
Shock	1	1	2	4
Nonresponsiveness	1	2	2	5
Ventricular fibrillation	0	1	0	1
Duration of pacing				
Days		6	1	14
Weeks	1	1	1	3
Outcome of pacing				
Recovery with normal sinus rhythm	3	5	2	10
With 2° or 3° A-V block	1	0	1	2
With permanent pacemaker	2	1	1	4
Death without pacing†	1	0	0	1
Death with pacing		1	3	6

[illegible]

†Catheterization was [illegible]

A V conduction defects a survey was made of the current experience of several prominent cardiologists (see Table III) We are indebted to Dr J Willis Hurst of Emory University School of Medicine (9 cases) Dr Thomas W Mattingly of Washington Hospital Center (2 cases) Dr Richard S Ross of The Johns Hopkins Hospital Dr Paul Yu of the University of Rochester Dr A V N Goodyer of Yale University Dr Franklin Johnston of the University of Michigan and Dr Carleton B Chapman of Parkland Hospital Dallas (1 case each) who reported the results of their own experience or that of their associates

Addendum

Since the preparation of this manuscript 2 more patients with complete A V heart block complicating acute inferior myocardial infarction have been treated promptly with catheter pacing Each had a return of normal sinus rhythm and each was discharged improved The over all mortality has diminished to 11 per cent

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Intractable Stokes-Adams disease

A method of emergency management

Benson B. Roe, M.D., F.A.C.S.
San Francisco, Calif.

Total heart block with Stokes-Adams attacks is often fatal, and the average life expectancy after the first attack is less than 2 years. Because both the occurrence of the attacks and the return of systolic action are unpredictable, the patient is rarely able to receive medical care in time for death to be averted. In our experience, most of the patients who do survive frequently recurring or intractable Stokes-Adams attacks (usually by taking an *inotropic drug which they keep available*) can be satisfactorily supported with intravenous isoproterenol, which stimulates a ventricular focus. However, this drug causes ventricular fibrillation in patients with highly irritable ventricles, and other patients unresponsive to it do not maintain a satisfactory ventricular rate. Until an implantable pacemaker can be inserted, such patients must be supported by an external pacemaker.

The electrical impulse from an external pacemaker can be carried to the heart either through the chest wall via skin *electrodes as described by Zoll[1] or through* a cardiac catheter as advocated by Parsonnet and Schwedel[2]. Although either method may prove to be effective, each has important disadvantages.

The external electrodes deliver a distinctly uncomfortable and frequently painful shock to the skin at the point of contact. Because of the high resistance of the skin a larger current is required, which may re-



Fig. 1. Close-up view of needle and electrode.



Fig. 2. Cutaway view of a dog heart showing left ventricular chamber with one wire still in place (*left*) and the second wire (*right*) after being withdrawn. Arrow (*right*) points to site of puncture ... which the wires were inserted during ...

From the Department of Surgery, University of California Medical School, San Francisco, Calif.
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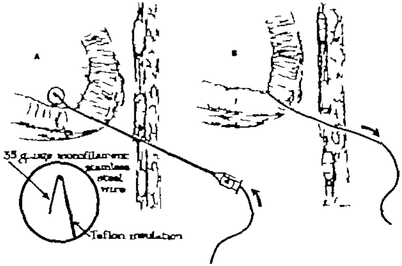
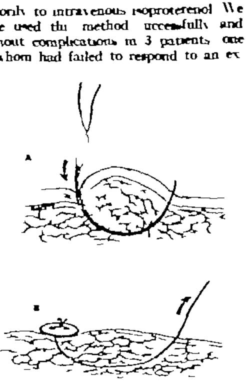


Fig 3 Schematic representation of method of inserting myocardial electrode wire A No 18 gauge pinal needle is directed percutaneou ly into the left en tricular chamber The hooked wire is inserted throu h the needle B The needle is withdrawn and the hook engaged into the endocardium This wire then attached to the negativ pole of an external pacemaker

sult in trouble-ome contractions of the musculature of the chest wall In obese patients with even greater skin resistance it may be impossible to stimulate a cardiac contraction even with maximal output Furthermore the presence of an external skin electrode on the chest wall at the time of surgical implantation of an internal pacemaker interferes with proper sterili zation of the skin and draping of the opera tive site

The catheter electrode may cause second ary thromboembolic phenomena Prophy lactic anticoagulation may prevent this complication but it in turn may threaten safe surgical implantation of a pacemaker There is also some ri k of introducing intravascular sep is through the sinus tract A further disadvantage is the neces ity for moving a critically ill patient to a catheterization laboratory for fluoroscopic guidance of the electrode into the heart In some instances ventricular fibrillation may be triggered by the intracardiac timulus

Because of these disadvantages we have favored the use of a percutaneous left ven tricular puncture to introduce a small insulated wire that maintains direct stimu lation in patients not responding satis factorily to intravenous isoproterenol We have used thi method uccessfully and without complications in 3 patients one of whom had failed to respond to an ex



F. 4 A Implantatio of ubcutaneou ind fferent electrode attached to positive pole of pacemaker B Insulated w re is denuded onl in the segment beneath the kin and ulated t both area of penetration

ternal pacemaker and had repeatedly developed ventricular fibrillation when a catheter electrode was inserted.

Method

A thin-walled No. 18 spinal needle is introduced percutaneously over the apical impulse and is directed toward the tip of the right scapula. As the left ventricle is entered, the obturator of the needle is withdrawn in order to verify its presence in the lumen. A fine (Grade 35) monofilament stainless steel wire insulated with Teflon is then introduced through the needle (Fig. 1). The terminal 15 mm. of the wire is bared and kinked back upon itself so that a doubled end is introduced through the needle. The needle is then withdrawn over the wire, which is pulled back so that its end can be engaged as a somewhat pliable barb against the endocardium (Figs. 2 and 3). Fixation to the skin is maintained with a suture and a tape flag. The wire is attached to the negative pole of an external pacemaker and the positive pole is grounded to an indifferent electrode. In an emergency, an ordinary skin electrode placed with conductive paste can be used for the indifferent site, but for longer maintenance we prefer to use a wire inserted subcutaneously (Fig. 4).

Although this method carries a slight hazard (but one as yet not experienced) of pericardial tamponade through puncture of a coronary artery at the apex, it has the advantage of providing an effective contact to the heart that can be introduced at the bedside with a minimum of delay. It is not recommended for long-term stimulation and should be replaced with an implantable pacemaker as soon as practicable. The presence of the wire at the operative site traversing the incision has not proved to be the problem that we expected, since it is possible to drape over the puncture site and to dissect around the wire while entering the chest. As a precautionary measure, an additional sterile needle-electrode is maintained in the operative field in case the wire should become dislodged.

Summary

A method is described for rapid percutaneous implantation of a myocardial electrode for temporary external electrical pacing prior to implantation of an internal pacemaker. This technique is useful in patients who cannot be satisfactorily controlled with intravenous isoproterenol and would appear to be preferable to the alternative techniques of transcutaneous or transvenous stimulation.

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The use of the Valsalva maneuver to differentiate fixed-orifice aortic stenosis from muscular subaortic stenosis

*Frank I. Marcus, M.D.**
*Robert C. Jones, M.D., F.A.C.P.***
Washington, D. C.

Patients with muscular hypertrophy of the left ventricular outflow tract commonly present with signs and symptoms simulating fixed valvular aortic stenosis. The points of differentiation favoring muscular subaortic stenosis are the apical location of the systolic murmur, the quick rising or double peaked peripheral pulse contour, the absence of an aortic ejection sound, and the lack of a diastolic murmur of aortic insufficiency.[1,2] In the chest roentgenogram of the patient with muscular subaortic stenosis, aortic valvular calcification will not be present, and poststenotic dilatation of the aorta will seldom be seen. Nevertheless, it is often difficult to be certain of the type of left ventricular outflow obstruction after thorough clinical evaluation. Laboratory procedures used to differentiate muscular subaortic stenosis from fixed orifice aortic stenosis include left ventricular angiocardiography,[3] as well as a decrease in the amplitude of the peripheral pulse after a premature beat.[4]

One of us (F. I. M.) observed that the Valsalva maneuver serves to accentuate the degree of outflow obstruction in patients with muscular subaortic stenosis.[5] It was suggested that in patients with fixed orifice aortic stenosis the Valsalva maneuver should not cause an increase in the degree of obstruction.[6] Rather, with a diminished flow across the valve, the left ventricular–aortic systolic gradient should decrease. Thus, the difference in hemodynamic response should differentiate these two conditions. Similar observations were made by Braunwald and associates,[7] and their data were in agreement with this hypothesis.

It is the purpose of this paper to present our experience based on simultaneously recorded pressures in the left ventricle and in a peripheral artery in patients with fixed-orifice and muscular subaortic stenosis, in order to verify further that the hemodynamic response is of aid in differential diagnosis.

Case selection

From Jan. 1, 1963, to Jan. 1, 1964, the response to the Valsalva maneuver was recorded in 13 patients undergoing left heart catheterization for suspected aortic outflow obstruction. Ten with fixed stenosis and 3 with muscular subaortic stenosis were encountered.

Of those with fixed-orifice stenosis, 3 have undergone surgery. Two had valvular

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*Markle Scholar in Medical Science; Assistant Professor of Medicine, Georgetown University School of Medicine [illegible] of Cardiology, Georgetown University Medical Division, District of Columbia General Hospital, Washington, D. C.
**[illegible] Chief of Cardiology, Walter Reed Army Medical Center, Washington, D. C.

Table I. Hemodynamic data before and during Valsalva maneuver

	At rest			During Valsalva maneuver			
Patient	LV systolic pressure (mm Hg)	Arterial systolic pressure (mm Hg)	LV-arterial systolic gradient (mm Hg)	LV systolic pressure (mm Hg)	Arterial systolic pressure (mm Hg)	Change in LV systolic pressure (mm Hg)	Change in arterial systolic pressure (mm Hg)
Muscular Subaortic Stenosis							
R. H.	118	118	0	133	99	+15	−19
A. H.	155	158	0	200	125	+4	−33
M. B.	184	104	80	214	9	+30	−17
Fixed Orifice Aortic Stenosis							
M. A.	110	106	4	104	95	−64	−2
R. W.	172	150		160	147	−12	−3
R. D. H.	143	115	28	173	98	−70	−17
E. D.	155	11	38	130	83	−75	−29
F. J. G.	1	140	4	12	113	−45	−1
C. C.	1 5	129	46	180	143	+5	+16
C. J. F.	160	96	64	130	8	−30	−18
I. R. S.	1 1	100	1	170	80	−51	−20
I. D. A.	20	140	80	183	105	−35	−37
N. S. C.	40	95	145	175	95	−65	−30
No Left Ventricular Outflow Obstruction							
S. C.	135	135	0	102	10	−33	−33
D. A.	120	125	0	8	8	−42	−47

lesions and one had a subvalvular diaphragm. Seven others with fixed orifice obstruction had clinical and hemodynamic findings in accord with this type of lesion. All but one (Patient F. D.) had either an aortic ejection sound, an aortic diastolic murmur, or poststenotic aortic dilatation—findings exceedingly uncommon in patients with muscular subaortic stenosis. The pulse pressure after the premature beat increased in all of the patients with fixed orifice stenosis.

Two of the 3 subjects with muscular subaortic stenosis (A. H. and R. H.) had diagnostic left ventricular angiocardiograms. Patient A. H. was the subject of a previous report.[4] In the third patient the diagnosis was verified by the reproducible decline in the pulse pressure after the premature beat.

Two patients presented clinically with features that were suggestive of muscular subaortic stenosis. They illustrate the response of the Valsalva maneuver in the individual without left ventricular outflow obstruction, since a left ventricular-aortic systolic gradient could not be demonstrated at rest, nor could obstruction be elicited after the inhalation of amyl nitrite[8] or by the infusion of isoproterenol at a rate of 3 µg per minute.[9,11]

Methods

The patients were studied in either the cardiovascular laboratories of the District of Columbia General Hospital or the Walter Reed Army Medical Center.* Left heart catheterization was performed by the retrograde femoral or by the transseptal technique. Simultaneous left ventricular and arterial pressures were inscribed on an Electronics for Medicine recorder using P23Db Statham strain gauges.

The Valsalva maneuver was performed with the patient in the supine position. In children under 10 years of age increased intrathoracic pressure was produced by

*Patient M. B. was catheterized by Dr. M. Clark, Jr., Georgetown University Hospital.

the anesthetist exerting pressure on the breathing bag for 15 to 20 seconds. Although intrapleural pressures were not measured, the degree of straining was adequate as indicated by the rise in ventricular end diastolic pressure.[1] The systolic pressures were measured immediately prior to straining, during peak Valsalva effect when the brachial arterial pulse pressure showed maximum decline, and after release of straining.

It was noted that during performance of the Valsalva maneuver the patient may move or tense the muscles of the extremities sufficiently to alter the position of the arterial needle and cause interference with adequate transmission of the pressure. The damped arterial pulse pressure recorded will read erroneously low and lead to the interpretation of an increase in the systolic gradient when no increase exists. This pitfall may be avoided by instructing the patient to avoid tension of the muscles of the extremities during straining and by observation of the needle in the peripheral vessel while the test is being performed.

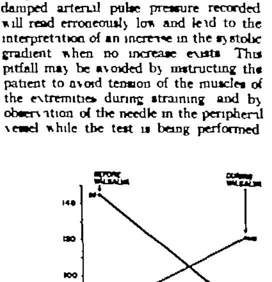


Fig. 1. Change in left ventricular-arterial systolic gradient before and during the Valsalva maneuver. The striking increase in gradient observed in patients with muscular subaortic stenosis contrasts with the unchanged or decreased gradient in those with fixed-orifice aortic stenosis.

Results

The data summarized in Fig. 1 and Table I indicate that the hemodynamic response in the patients with muscular subaortic stenosis differs from that observed in patients with fixed orifice aortic stenosis. In the 3 patients with muscular obstruction, there was an increment of 15 to 42 mm. Hg in left ventricular systolic pressure during peak Valsalva effect. In contrast, the patients with fixed-orifice stenosis with one exception (Patient G. C.) demonstrated a decline in left ventricular systolic pressure. Characteristic responses are illustrated in Figs. 2 and 3. In patients in all categories excluding Patient G. C., the arterial systolic pressure fell. The divergence in left ventricular and arterial pressures in the group with muscular subaortic stenosis resulted in an increase in the left ventricular outflow pressure gradient (Fig. 1). With fixed orifice stenosis the left ventricular and brachial arterial systolic pressures were altered in parallel. Usually, the left ventricular systolic pressure declined more than the arterial pressure and the systolic gradient diminished.

Discussion

The response to the Valsalva maneuver was observed to differ in subjects with fixed orifice aortic stenosis as compared to those with muscular subaortic stenosis.

In the presence of fixed orifice aortic stenosis the decrease in venous filling of the heart during straining results in a marked decrease in stroke output.[7] As flow diminishes across the fixed obstruction, both left ventricular and aortic systolic pressures fall. Usually, left ventricular pressure falls disproportionately since the relationship of gradient to flow is such that, as the flow is halved, the gradient will fall to one fourth of the original value.[13]

The unique response of Patient G. C. deserves comment. This patient with stenosis of the tricuspid, mitral, and aortic valves responded to straining by an increase in both left ventricular and brachial arterial systolic pressures. This "square wave" response has been described in patients with congestive heart failure as well as in those with large atrial septal defects.[14,15] Since the "square wave" response

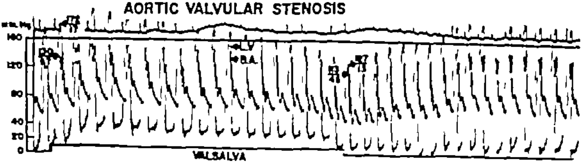


Fig. 2. Left ventricular (*L.V.*) and brachial arterial (*B.A.*) pressure pulses recorded simultaneously during the performance of the Valsalva test in patient L. I. C. with aortic stenosis and insufficiency. Note the concomitant fall in both pressures. There [illegible] disappearance of the [illegible] pulse in the brachial arterial pressure tracing. Paper speed of 25 mm. per second.

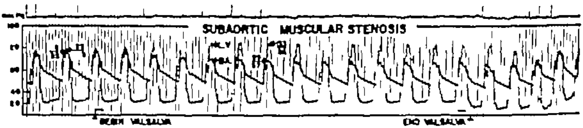


Fig. 3. Circulatory response to straining in Patient K. H. with muscular subaortic stenosis. The characteristic brachial arterial (*B.A.*) pressure pulse contour was elicited at peak Valsalva response. *L.V.*, Left ventricular pressure pulse. Paper speed of 25 mm. per second.

can be reproduced in normal individuals after rapid infusion of whole blood or abolished in patients with congestive heart failure when cuffs are inflated on the extremities; it is thought to be related to a large central blood volume or increased total intravascular volume.[13,14] Although the left ventricular systolic pressure increased with straining in this patient with valvular aortic stenosis, both the left ventricular and arterial systolic pressures rose concomitantly. There was a decrease of 11 mm. Hg in the gradient. Therefore, the square wave response in a patient with fixed-orifice aortic stenosis can readily be differentiated from the divergent left ventricular and arterial pressures observed during straining in patients with muscular subaortic stenosis.

The increased obstruction seen in the presence of muscular subaortic stenosis during straining may be explained by a diminution in venous return, which results in a decrease in cardiac dimensions and a further approximation of the already narrowed outflow tract.[8] It would be anticipated that left ventricular systolic pressures would rise during the Valsalva maneuver as a consequence of increased obstruction, and this was observed in the 3 patients with this condition. However, this response may be modified by other factors, such as the contractile properties of the myocardium in response to the vagal stimulation induced by straining, as well as by the degree of change in the peripheral resistance. This may be the explanation for the variable response of the left ventricular systolic pressure during peak Valsalva effect observed by others.[7] Nevertheless, the disproportionate fall in arterial pressure that yields an increased systolic gradient has been a consistent finding.

The characteristic hemodynamic responses to the Valsalva maneuver as described in this paper and by others[7] have been consistent and should therefore be

useful in differentiating muscular subaortic from fixed orifice aortic obstruction

In previous publications it was demonstrated that the Valsalva test was of aid in establishing the diagnosis of muscular subaortic stenosis in a patient who did not have a left ventricular–brachial artery systolic gradient during the control period[6,7] This was confirmed in Patient R H in whom a diagnostic gradient was induced during straining (Fig 3) In this patient as in Patient A H the subject previously reported on[6] there was an increase in the peripheral pulse pressure after the premature beat at rest but a decrease just after release from straining This observation demonstrated that the paradoxical decrease in the pulse pressure after the premature beat although characteristic of the response seen in patients with muscular subaortic stenosis may not be present when the patient is in the control state because of the variable degree of outflow obstruction

During the performance of the Valsalva maneuver it is instructive to study the contour of the peripheral pulse as the amplitude decreases In the patient with fixed valvular aortic stenosis the dicrotic notch is lowered and disappears as it reaches the diastolic pressure In patients with valvular aortic stenosis and aortic insufficiency the second peak of the bisferiens pulse diminishes and eventually disappears as the amplitude of the pulse decreases[7] (Fig 2) In contrast in patients with muscular subaortic stenosis the double peaked contour remains or may appear at the height of the Valsalva test (Fig 3) The relative position of the dicrotic notch is not significantly changed during straining These observations suggest that evidence of muscular subaortic stenosis can be obtained by the direct recording of the peripheral pulse at rest and during the Valsalva maneuver in a patient suspected of having this entity

Currently the protocol used to diagnose muscular subaortic stenosis is as follows Left ventricular and peripheral pulse pressures are recorded simultaneously If a systolic gradient is present premature ventricular beats are induced If the pulse pressure after the premature beat is diminished the diagnosis of muscular subaortic stenosis is established The type of outflow obstruction is further verified by the response to the Valsalva maneuver

If a gradient is not observed the patient inhales amyl nitrite and the left ventricular and peripheral pulses are continuously recorded[6] If no gradient is induced it is considered unlikely that left ventricular outflow obstruction is present since this provocative test has been observed to be more sensitive than either isoproterenol or straining in evoking a gradient[14] If a systolic gradient is seen it is interpreted as evidence of outflow obstruction of undetermined type since a similar response is observed in fixed-orifice aortic stenosis The response to the Valsalva maneuver is then used in order to differentiate fixed orifice aortic stenosis from muscular subaortic stenosis Further verification of the nonfixed nature of the obstruction may be obtained by observing the response after the premature beat during the height of amyl nitrite effect

Intravenous isoproterenol may also be used to induce a gradient in muscular subaortic stenosis[6,11] but amyl nitrite is preferred since the latter drug is less likely to induce ventricular ectopic beats and since it is probably more sensitive than isoproterenol in eliciting evidence of left ventricular obstruction Nitroglycerin may be substituted for amyl nitrite[7] However amyl nitrite is preferred to nitroglycerin since the left ventricular–systolic arterial gradient induced by amyl nitrite is of short duration With nitroglycerin an unexpectedly long effect sometimes accompanied by chest pain has been observed During the peak effect of the drugs employed inspection of the contour of the peripheral pulse adds confirmation with regard to the type of outflow obstruction

Summary

The response to the Valsalva maneuver was observed in 10 patients with fixed-orifice aortic stenosis and 3 patients with muscular subaortic stenosis In the patients with fixed orifice aortic stenosis the peak systolic gradient either remained essentially unchanged or decreased This was due to a decrease in left ventricular systolic pressure equal to or greater than the decline in arterial pressure

In the subjects with muscular subaortic stenosis the peak systolic gradient increased with straining, an effect caused by a rise in left ventricular systolic pressure while arterial systolic pressure declined. The mechanism for the difference in the responses was discussed.

The peripheral pulse tracing during the Valsalva maneuver was found to differ in contour in the two groups studied.

The conclusion is that the response to the Valsalva maneuver is of aid in the hemodynamic differentiation of fixed orifice aortic stenosis from muscular subaortic stenosis.

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Evaluation of left heart disease by statistical analysis of aortic parameters and transverse cardiac diameter

*Jon E. Gustafson, M.D.**
Marvin J. Friedenberg, M.D.
St. Louis, Mo.

There is a group of congenital and acquired cardiovascular abnormalities characterized by an increase in the size of the thoracic aorta and/or some form of disease of the left ventricle. The most frequent of these pathologic conditions are hypertensive cardiovascular disease, occlusive coronary artery disease, aortic valve stenosis or insufficiency, and coarctation of the thoracic aorta.[1] The following is a report of a statistical analysis of the transverse cardiac diameter and aortic parameters in selected groups of adult patients with these diseases, including matched sets of normal patients for control purposes.

Materials

All patients studied were at least 21 years old and had a satisfactory posteroanterior chest roentgenogram taken at a distance of 72 inches in the erect position. No patient was accepted whose chest roentgenogram showed rotation, scoliosis, congestive heart failure, incomplete inspiration, or an unusual mass or infiltrate which obscured the aortic and/or cardiac margin. Thirty-eight patients with hypertensive cardiovascular disease were accepted for study. All of these patients had a persistent diastolic blood pressure of 100 mm. Hg or greater, an electrocardiographic pattern free of ischemia, injury, or infarction, and no evidence of valvular heart disease. Thirty-nine patients with occlusive coronary artery disease were studied. All were discharged from the hospital with an electrocardiogram proved diagnosis of myocardial infarction, and none ever had a diastolic blood pressure greater than 90 mm. Hg. Twelve patients with aortic stenosis were studied, 13 with aortic insufficiency, and 7 with coarctation of the aorta. These patients were accepted for study only if their diagnoses were proved by cardiac catheterization and angiocardiography and/or cardiovascular surgery. None of these patients were included if they had a myocardial infarction or hypertension. (The latter criterion did not apply to patients with coarctation of the aorta.)

For each of the above mentioned patients a normal control patient was examined, matched according to age, sex, and weight. The patients in the control groups had routine chest roentgenograms and had no evidence of hypertension, myocardial infarction, or aortic valve disease.

Methods

In all patients the following measurements were made in the posteroanterior

From The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo.
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Table I. Comparison of thoracic width (TT) and age in diseased and normal subjects

	Hypertensive cardiovascular disease	Coronary occlusive disease	Aortic valve stenosis	Aortic valve insufficiency	Coarctation of thoracic aorta	Total control group
TT	28 6	29 6	28 0	[illegible]	[illegible]	[illegible] 8
	4	48	85	[illegible]	5[illegible]	30
Age	50 9	60 4	40 7	3[illegible] 0	35 1	44 9
	1 8	1 85	2 78	3 24	4 33	1 0

*TT values are given in centimeters

Table II. Comparison of the transverse cardiac diameter (TH) in diseased subjects and their matched controls

	Hypertensive cardiovascular disease	Coronary occlusive disease	Aortic valve stenosis	Aortic valve insufficiency	Coarctation of thoracic aorta
Diseased					
Mean	15 3	14 4	13 8	16 2	14 2
S	49	1 4	1 75	2 34	1 70
Range	9 5 21 0	10 1 18	10 5 15	12 20 5	12 5 18
Control					
Mean	1 9	13 4	11 9	1 5	11 8
S	1 [illegible]	1 45	1 91	1 67	2 01
Range	9 4–16 5	10 5–16 0	9 0–15 0	10 0 15	9 5 14 4
t	4 89		53	4 68	31
P	< 01	< 01	< 05	< 05	< 05

*Significant p values are indicated by [illegible]. All values are given in centimeters.

roentgenogram of the chest (Fig 1) transverse diameter of the thorax (TT) at the level of the dome of the right diaphragm transverse diameter of the heart (TH) defined as the sum of the greatest cardiac distances to the right (THR) and to the left (THL) of the midline height of the aorta (AH) defined as the distance between the right cardiovascular junction and the tip of the aortic knob prominence of the aorta (AI) defined as the greatest aortic width to the left of the midline at the level of the aortic knob and width of the aorta (AR) defined as the greatest width of the ascending aorta to the right of the midline

The data were analyzed for differences between groups and possible relationships of one variable to another Calculations included the determination of correlation coefficients and t values and the analysis of covariance (in order to correct for differences in age between groups)

Results

The transverse diameter of the thorax was remarkably similar in all patients examined (Table I) However the average age of the patients with the five diseases studied differed The oldest patients were those with coronary occlusive disease (average 60 4 years) and the youngest had coarctation of the thoracic aorta (average 35 1 years) Patients with disease showed the following changes relative to their matched normal controls All patients with disease had a statistically significant increase in transverse heart diameter (Table II) The width of the ascending aorta was greater to a statistically

significant degree in all patients with disease except for those with occlusive coronary artery disease (Table III). There was a statistically significant increase in the prominence of the aortic knob in patients with hypertensive cardiovascular disease but this was not true in any of the other patients (Table IV). The hypertensive patients also were the only ones whose aortic height was significantly greater than that of their matched normal controls (Table V).

Thus relative to their matched normal controls patients with hypertensive cardiovascular disease had a statistically significant increase in heart size, prominence of the ascending aorta, height of the aorta and size of the aortic knob. Patients with occlusive coronary artery disease had a statistically significant increase in heart size but not in the aortic parameters. Patients with aortic stenosis, aortic insufficiency, or coarctation of the aorta had a statistically significant increase in cardiac size and prominence of the ascending aorta but the height of the aorta and prominence of the aortic knob were within normal limits.

Discussion

Average values for the various heart dimensions have been measured in large groups of normal individuals[1] and various formulas have been devised for determining the normal transverse diameter[3] and frontal area[4] of the heart according to the age, weight, and height of the patient. These cardiac dimensions have been used as

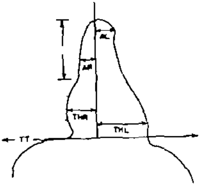


Fig. 1. Line drawing of central cardiovascular outline indicating dimensions analyzed. *TT*, Transverse diameter of the thorax at the level of the dome of the right diaphragm. *THR*, Greatest cardiac distance to the right of midline. *THL*, Greatest cardiac distance to the left of midline. *AH*, Height of the aorta, defined as the distance between the right cardiovascular junction and the top of the aortic knob. *AL*, Prominence of the aorta, defined as the greatest aortic width to the left of the midline at the level of the aortic knob. *AR*, Width of the aorta, defined as the greatest width of the ascending aorta to the right of the midline. *TH*, Transverse diameter of the heart obtained by adding THR and THL.

Table* III. *Comparison of the width of the ascending aorta (AR) in diseased subjects and their matched controls

	Hypertensive cardiovascular disease	*Coronary occlusive disease*	*Aortic valve stenosis*	*Aortic valve insufficiency*	*Coarctation of thoracic aorta*
Diseased					
Mean	3 2	3 0	2 9	3 3	3 1
S	98	83	74	1 38	83
Range	1 3–4 9	1 6–5 0	1 7–4 3	1 [illegible]–6 9	2 4–4 3
Control					
Mean	3	2 8	3	2 2	[illegible] 3
S	41	55	59	29	53
Range	1 6–3 5	1 9–4 0	1 5–3 6	1 8– 9	1 7 [illegible] 0
t	5 [illegible]	1 25	2	8	[illegible] 16
P	< 01	> 10	< 05	< 01	< 05

[illegible]

Table IV. Comparison of the prominence of the aortic knob (AK) in diseased subjects and their matched controls

	Hypertensive cardiovascular disease	*Coronary occlusive disease*	*Aortic valve stenosis*	*Aortic valve insufficiency*	*Coarctation of thoracic aorta*
Diseased					
Mean	4 1	3 [illegible]	3 1	3 1	2 9
S	78	66	4?	61	39
Range	2 5 6 0	2 1 5 1	2 3 3 8	2 0 4 5	2 4 3 4
Control					
Mean	3 2	3 5	8	3 0	2 [illegible]
S	55	4?	53	5[illegible]	8
Range	2 3 5 1	2 (4 5	2 0 3 (	2 1 4 0	2 0-4 3
t	5 6	7	1 43	43	61
p	< 01	> 10	> 10	> 10	> 10

Significant p values are indicated by an asterisk. All values are given in centimeters.

Table V. Comparison of the height of the aorta (AH) in diseased subjects and their matched controls

	Hypertensive cardiovascular disease	*Coronary occlusive disease*	*Aortic valve stenosis*	*Aortic valve insufficiency*	*Coarctation of thoracic aorta*
Diseased					
Mean	9 8	10 0	9 5	9 9	9 5
S	1 34	1 31	1 45	2 36	1 67
Range	7 3 13 7	7 5 14 2	5-11 8	6 0 14 0	7 0 11 5
Control					
Mean	8 8	9 6	8 4	9 1	8 4
S	1 18	1 16	1 18	1 37	81
Range	7 0 11 5	7 5 12 0	6 6-10 2	7 1 11 3	7 1-9 2
t	3 45	1 8	2 04	1 07	1 55
p	< 01	< 10	< 10	> 10	> 10

Significant p values are indicated by an asterisk. All values are given in centimeters.

criteria for distinguishing normal and abnormal hearts[4] and for differentiating among the principal categories of heart disease.[4,5] Many investigators believe that prediction formulas which consider the subject's age and size are the best methods for determining his degree of normalcy,[9,10] whereas others attribute less value to measurement of heart dimensions and emphasize the importance of the shape of the cardiac silhouette.[11]

The relationship of the width and length of the aorta is reported to differ in various types of heart disease.[3] The principal difficulty in measuring the aorta is in determining its borders, the margins of which may be obscured by other mediastinal contents. Because of the impossibility of determining accurately the width of the ascending aorta[1] in plain roentgenograms of the chest, the left anterior oblique projection has been used to help estimate its size.[12] Numerous parameters have been used in evaluation of the aortic size, including the sum of the widest supracardiac shadow to the right of the midline and the

widest portion of the aortic knob to the left of the midline, the distance between the right cardiovascular junction and the height of the aortic knob, the distance between the inferior margin of the clavicle and the top of the aortic knob, the length of the chord subtended by the arc of the aortic arch in the left anterior oblique projection, and the width of the aortic knob as determined with barium filling the adjacent esophagus. Complete examination of the aorta requires determination of its length, width, course, density, pulsation, and mobility. In this report we consider only the width and length of the aorta in a posteroanterior chest roentgenogram. We recognize the inherent inability of distinguishing accurately aortic dilatation from elongation.

In normal individuals the aortic width correlates most closely with the patient's age (r = .30) and only slightly with the patient's weight (r = .14).[19] The width of the aorta has been reported to increase approximately 1 mm. per 3 years in individuals over 43 years of age.[19] This finding was confirmed in our patients by analysis of the aortic measurements, all of which increased progressively with age. In our patients the width of the ascending aorta (AR), the prominence of the aortic knob (AL), and the height of the aorta (AH) increased 0.1, 0.2, and 0.4 millimeters, respectively, per year (Table XI).

Since all aortic dimensions are dependent on age, their measurement in any given patient must be interpreted first with respect to the age of the patient. Table XI gives the formulae which may be used to predict the normal aortic parameters according to age. Table VI gives the aortic parameters and transverse cardiac di-

Table VI. Relationship of age adjusted means of aortic parameters and transverse cardiac diameters (expressed in descending order of magnitude)

Width of ascending aorta (AR)		t	Prominence of aortic knob (AL)		t	Height of aorta (AH)		t	Transverse cardiac diameter (TD)		t
Aortic valve insufficiency	3.3 (3.3)	38	Hypertensive cardiovascular disease	4.0 (4.1)	13	Aortic valve insufficiency	10.2 (9.9)	66	Aortic valve insufficiency	16.3 (16.2)	65
Coarctation of thoracic aorta	3.2 (3.1)	31	Coronary occlusive disease	3.3 (3.6)	11	Coarctation of thoracic aorta	9.9 (9.5)	64	Hypertensive cardiovascular disease	15.2 (15.3)	40
Hypertensive cardiovascular disease	3.2 (3.2)	16	Aortic valve stenosis	3.2 (3.1)	14	Aortic valve stenosis	9.7 (9.8)	42	Coarctation of thoracic aorta	14.3 (14.2)	7?
Coronary occlusive disease	2.9 (3.0)	13	Aortic valve insufficiency	3.2 (3.1)	17	Hypertensive cardiovascular disease	9.6 (9.8)	22	Coronary occlusive disease	14.2 (14.4)	28
Aortic valve stenosis	2.9 (2.9)	21	Coarctation of thoracic aorta	3.1 (2.9)	15	Coronary occlusive disease	9.4 (10.1)	22	Aortic valve stenosis	13.9 (13.8)	51
Total control group	2.4	05	Total control group	3.0	06	Total control group	8.9	11	Total control group	12.5	17

[illegible]

Table VII. Significance of comparison of the width of the ascending aorta (AR) between disease groups

		Aortic valve insufficiency 3.3	Coarctation of the aorta 3.2	Hypertensive cardiovascular disease 3.2	Coronary occlusive disease 4
Coarctation of the aorta	3.2	F 1.43 p > .05			
Hypertensive cardiovascular disease	3.2	F .46 p > .05	F .29 p > .05		
Coronary occlusive disease	2.9	F 3.01 p > .05	F .86 p > .05	F 1.45 p > .05	
Aortic valve stenosis	2.9	F 1.38 p > .05	F 1.30 p > .05	F 1.01 p > .05	F 0.0 p > .05

[illegible]

Table VIII. Significance of comparison of the prominence of the aortic knob (AK) between disease groups

		Hypertensive cardiovascular disease 4.0	Coronary occlusive disease 3.3	Aortic valve stenosis 3	Aortic valve insufficiency 3.2
Coronary occlusive disease	3.3	F 18.8 p < .01			
Aortic valve stenosis	3.2	F 8.56 p < .01	F .89 p > .05		
Aortic valve insufficiency	3	F 7.48 p < .01	F .48 p > .05	F 0.0 p > .05	
Coarctation of the aorta	3.1	F 11.64 p < .01	F 4.42 p < .05	F 2.75 p > .05	

[illegible]

ameter corrected for age in patients with the five diseases studied and also in the matched normal controls analyzed as a single group. The relationships are expressed in descending order of magnitude. In the absence of right heart and/or marked left atrial enlargement and in the absence of abnormalities of the pulmonary vessels the vast majority of patients with a transverse cardiac diameter greater than 13 cm. have one of the five diseases analyzed in this study. The increased transverse cardiac diameter of these patients distinguishes them from normal individuals with a high degree of reliability (Table II). Analysis of the aortic dimensions in these patients then provides a method of using the size of the aorta as a guide in determining the type of left ventricular disease present.

In a comparison of the disease groups the single most significant finding is the marked prominence of the aortic knob in patients with hypertensive cardiovascular disease (Table VI). There is a high degree of probability ($p < .01$) that hypertensive

cardiovascular disease is present in a group of patients with a mean aortic knob dimension of 3.8 cm. or greater (Table VIII). Tables VII-X further express the relationships of the transverse heart diameters and aortic parameters in patients with hypertensive cardiovascular disease and the four other diseases studied. The tables show that the transverse cardiac diameter and aortic parameters may be

Table IX. Significance of comparison of the height of the aorta (AH) between disease groups

		Aortic valve insufficiency 10.2	*Coarctation of thoracic aorta 9.9*	*Aortic valve stenosis 9.7*	*Hypertensive cardiovascular disease 9.6*
Coarctation of thoracic aorta	9.9	F 1.29 $p > .05$			
Aortic valve stenosis	9.7	F .57 $p > .05$	F .56 $p > .05$		
Hypertensive cardiovascular disease	9.6	F 3.07 $p > .05$	F 2.50 $p > .05$	F .21 $p > .05$	
Coronary occlusive disease	9.4	F 1.99 $p > .05$	F 1.39 $p > .05$	F 0.0 $p > .05$	F .23 $p > .05$

*Significant p values are indicated by asterisk.

Table X. Significance of comparison of the transverse cardiac diameter (TH) between disease groups

		Aortic valve insufficiency 16.3	*Hypertensive cardiovascular disease 15.2*	*Coarctation of thoracic aorta 14.3*	*Coronary occlusive disease 14.?*
Hypertensive cardiovascular disease	15.2	F 1.08 $p > .05$			
Coarctation of thoracic aorta	14.3	F .46 $p > .05$	F .59 $p > .05$		
Coronary occlusive disease	14	F .7 $p < .01$	F 3.28 $p > .05$	F 1.01 $p > .05$	
Aortic valve stenosis	13.9	F 9.33 $p < .01$	F 2.87 $p > .05$	F .52 $p > .05$	F 1.42 $p > .05$

*Significant p values are indicated by asterisk.

Table XI. Formulae for predicted normal aortic parameters based upon age

1. Prominence of aortic knob (AL) $Y = 3.0 + .07 (x - 45)$
2. Height of aorta (AH) $Y = 8.9 + .043 (x - 45)$
3. Width of ascending aorta (AR) $Y = 2.4 + .007 (x - 45)$

Where x = age of patient in years

used to evaluate qualitatively these four diseases Thus aortic insufficiency is characterized by marked cardiomegaly a relatively high aorta and an aortic knob which is only slightly prominent In general the other three diseases are characterized by cardiomegaly of lesser degree Coarctation of the aorta tends to be associated with an increase in the height of the aorta and the width of its ascending portion Other findings such as rib notching and the reversed three sign help establish the diagnosis Patients in whom the ascending aorta is only slightly prominent are likely to have occlusive coronary artery disease in the older age group and aortic stenosis in the younger age group (Table I)

Summary and conclusions

1 The transverse cardiac diameter and aortic parameters were measured in selected adult patients with hypertensive cardiovascular disease occlusive coronary artery disease aortic valve stenosis or insufficiency and coarctation of the thoracic aorta and these measurements also were made in matched normal controls

2 Patients with any one of the five diseases studied had a significantly greater transverse cardiac diameter than that of their controls

3 The height of the aorta was significantly greater in patients with hypertensive cardiovascular disease than in matched normal controls The aortic knob was significantly more prominent in patients with hypertensive cardiovascular disease than in normal patients and in patients with the other diseases

4 The transverse cardiac diameter aortic parameters and age of patients may be used to differentiate qualitatively occlusive coronary artery disease aortic valve stenosis or insufficiency and coarctation of the aorta

5 The foregoing conclusions are based on average values in groups of patients Although the trends elucidated are useful in evaluating patients with left ventricular and/or aortic enlargement these roentgenographic findings must be interpreted with respect to all available radiologic and clinical data

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Experimental and laboratory reports

The digital rheoplethysmogram in complete heart block in man

Nicholas P. DePasquale, M.D.
*George E. Burch, M.D.**
New Orleans, La.

The hemodynamic alterations associated with complete heart block in man include an increase in arterial systolic blood pressure, total systemic vascular resistance, pulse pressure, and stroke volume and a decrease in cardiac output and mean arterial blood pressure. These alterations have been studied fairly well by means of cardiac catheterization.[1] However, studies of the peripheral circulation in complete heart block have been few. Macgregor[2] described capillary pulsations in patients with complete heart block and attributed them to augmentation of the normal capillary pulse due to the high pulse pressure.

Because of the hemodynamic alterations associated with complete heart block, it was considered of interest to study rheoplethysmographically the digital circulation in patients with this conduction defect.

Materials and methods

Digital rheoplethysmograms (RPG) were obtained on 16 patients with complete heart block. Complete heart block was due to coronary (ischemic) heart disease in 14 of the 16 patients. In one patient the heart block was associated with rheumatic aortic stenosis and in another with congenital ventricular septal defect. In 3 patients with coronary heart disease and complete heart block, rheoplethysmograms were obtained before and after implantation of a cardiac electrode pacemaker.

For comparison, digital rheoplethysmograms were also obtained in a patient with sinus bradycardia and in another patient with a slow atrial fibrillation. In addition, the digital blood flow during the compensatory pause after a ventricular premature contraction was measured in the patient with sinus bradycardia.

The rheoplethysmographic technique used in this laboratory has been described in detail elsewhere.[3]

Results

Complete heart block. On the basis of the characteristics of the digital blood flow, the patients were divided into Group A and Group B.

GROUP A (9 PATIENTS). In this group the alpha and beta deflections were markedly reduced in magnitude. The volumes (I_V) and rates (I_R) of blood flow into the digit were low (Fig. 1). In spite of the fact that little blood entered the digit during the systolic phase of the pulse cycle, the I_V curve leveled off or declined during diastole (Fig. 1).

In 3 patients the simultaneous curves of inflow (I_V) and outflow (O_V) were widely

From the Department of Medicine, Tulane University School of Medicine, and the Charity Hospital of Louisiana, New Orleans, La.
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*Address: 1430 Tulane Ave., New Orleans, La., 70112.

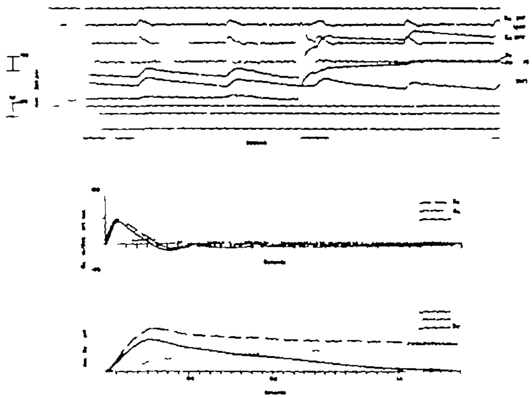


Fig. 1. Digital RIG of a 58 year-old white man with complete heart block. In this and all similar illustrations which follow, the original digital RIG recording is shown at the top. The simultaneous time course curves of the volume and rate of inflow, outflow, and difference between inflow and outflow for a single pulse cycle are shown below. *I* equals time course of digital inflow volume. *O* equals time course of digital outflow volume. *D* equals time course of the difference between inflow and outflow volumes (volume pulse wave). I_R equals time course of the rate of digital inflow. O_R equals time course of the rate of digital outflow. D_R equals time course of the difference between the rates of inflow and outflow. *2RF* refers to the second right finger and *3RF* to the third right finger. Note that although the volume of blood flowing into the digit is small, the I_V curve declines during the diastolic phase of the pulse cycle, indicating a tight digital venous system typical of Group A.

separated temporally. This separation was due primarily to a "lag" in the outflow curve.

The curve of the rate of inflow (I_R) of blood into the finger tip increased rapidly during the systolic phase of the pulse cycle and then fell rapidly to zero before the beginning of the diastolic phase of the pulse cycle (Fig. 1). Once the rate of outflow (O_R) exceeded the rate of inflow (I_R) during the cardiac cycle, it remained greater than I_R for the remainder of the pulse cycle (Fig. 1).

The magnitude of the maximal pulsatile flow, which is related to systolic filling, was at the lower limits of the range for normal subjects. However, the basal pulsatile flow, which is related to diastolic filling, was considerably reduced (Fig. 1).

GROUP B (7 PATIENTS). In this group the alpha and beta deflections were of the magnitude seen in normal subjects. The volumes (I_V) and rates (I_R) of inflow of blood into the digit, although less than normal, were considerably greater than those of Group A. Furthermore, in contrast to Group A, the curve of the inflow volume either continued to rise during the diastolic phase of the pulse cycle (Fig. 2) or leveled off as a result of a relatively large and rapid inflow of blood during systole (Fig. 3). A lag in the curve of the outflow volume was well developed in 2 patients (Fig. 4).

In Group B the curve of the rate of inflow (I_R) of blood into the finger tip rose rapidly during systole, remained elevated for about 0.1 second, fell gradually to

below the level of the outflow curve (O_R) and then rose again during early diastole but did not exceed O_R.

The maximal pulsatile flow was within the normal range. The basal pulsatile flow, although low, was greater than that for the patients in Group A.

Leveling off of the curve of inflow volume (I_V) during diastole is a result of "leakage" of blood out of the portion of the finger tip contained within the plethysmographic cup which occurs when the digital venous pressure exceeds the effective occluding pressure of the pneumatic cuff.[4] When the I_V curve becomes negative during diastole there is a decrease in the capacity of the collecting vessels due to venous constriction in addition to leakage past the occluding cuff. This phenomenon may occur as a result of two factors: (1) the digital venous reservoir may be "tight" because of increased venous tone, so that even a small increase in digital blood volume produces a marked increase in digital venous pressure; or (2) the digital venous reservoir may be "loose," but the volume of blood flowing into the digit during systole is so great that the pressure in the digital veins quickly rises above that of the pneumatic occluding cuff. *In the first instance* the digital collecting system is one of high pressure and low capacity, whereas in the second instance the digital collecting system is one of low pressure and high capacity.

In order to determine whether the curve of inflow volume leveled off because of a "tight" digital venous system or because of "overfilling" of a relatively loose digital venous system, composite curves of inflow rate and volume were constructed by measuring and plotting temporally nu-

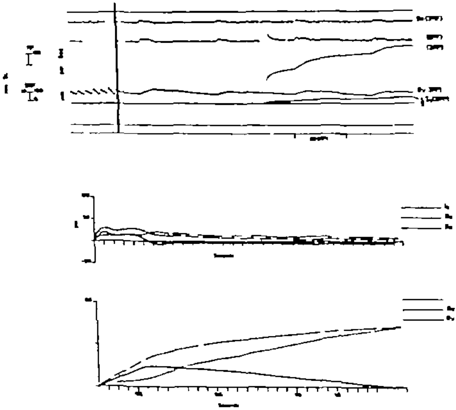


Fig. 2. Digital RPG of a 6 year-old Negro woman with complete heart block. Note that blood continues to accumulate in the finger tip during the diastolic phase of the pulse cycle, indicating a relatively loose digital venous system typical of Group B.

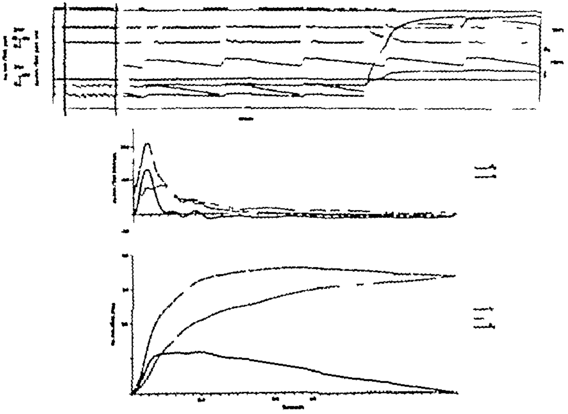


Fig. 5. Digital RFC of ... 3? ...ar-old ... man with complete heart block (Group B). Although the inflow volume ... during diastole, this ... due primarily ... refilling during systole rather than to a tight ...

...neous inflow rates and volumes at 0.05 second intervals within the pulse cycle obtained from a series of rheoplethysmographic recordings for the same digit in which venous obstruction was produced at various points of the pulse cycle.[3] The mean values at each 0.05 second of a pulse cycle were then obtained and mean I_V and I_R curves were constructed for an average pulse cycle. Construction of such curves indicated that the leveling off of the curve of inflow volume in Group A patients was due to the fact that no blood flowed into the finger tip during diastole (high pressure low reserve), whereas in Group B patients the blood did flow into the finger tip during diastole (low pressure high reserve) (Fig. 5). However, in the Group B patients only a portion of the total digital inflow volume during a pulse cycle could be accommodated by the digital veins before leakage past the collecting cuff occurred.

RPC after implantation of electrode pacemaker. In 3 patients digital RFC were obtained before and after implantation of a cardiac electrode pacemaker. In one patient, a 3? year old white man (Group B), implantation of the pacemaker resulted in a marked change in digital blood flow. Before implantation of the pacemaker virtually all of the blood flowed into the finger tip during systole (Fig. 3), whereas after implantation of the electrode the blood flowed into the finger tip during both phases of the pulse cycle (Fig. 6). In the other 2 patients, both of whom were in Group A, implantation of the cardiac electrode pacemaker resulted in an increase in digital blood flow, particularly during diastole (Fig. 7 *a* and *b*). Basal flow also increased after implantation of the electrode pacemaker.

Sinus bradycardia. The digital rheoplethysmogram was recorded in a normal subject with a cardiac rate of 40 beats per

minute In this subject the alpha and beta deflections were low in amplitude However blood accumulated in the collecting vessels of the finger tip during both phases of the pulse cycle after venous occlusion (Fig 8) The curve of outflow of blood (O_T) from the finger tip had an essentially normal temporal relationship with the simultaneously recorded curve of inflow (I_V) The rate at which blood flowed into the finger tip was low but it did not decline for almost 0.? second after reaching a maximum and when it did decline it did so gradually rising again in early diastole As expected the I_R curve reflected the persistent rise in the I_V curve

Blood flow during a premature ventricular beat Only the I_V and I_R curves of the premature beat were satisfactory for analysis (Fig 9) The curve of inflow volume (I_V) showed filling during both systole and diastole The mean rate of blood flow was normal and was higher than that for a preceding normal beat

Discussion

Patients with complete heart block could be readily separated into two groups on the basis of digital blood flow In one group of patients (Group A) the alpha and beta deflections as well as the volume and rate of inflow into the digit were reduced In addition most or all of the digital inflow occurred during systole The contour of the curve of digital inflow volume was of the type seen in patients with increased tone of the postcapillary blood vessels Because of the tightness of the postcapillary or collecting vessel little or no blood flowed into the finger tip during diastole after venous occlusion

In the second group of patients (Group B) the alpha and beta deflections were well developed The volume and rate of digital blood flow were greater than those of patients in Group A but were still not of the magnitude of those of normal subjects In addition blood continued to flow into the finger tip during diastole which

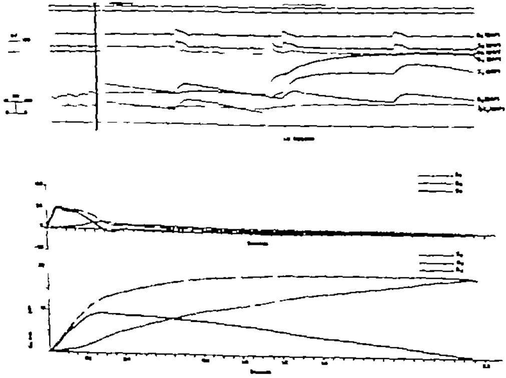


Fig 4 Digital RPC of a 66-year-old white man with complete heart block (Group B) Note the lag in the O curve Consult text for detail

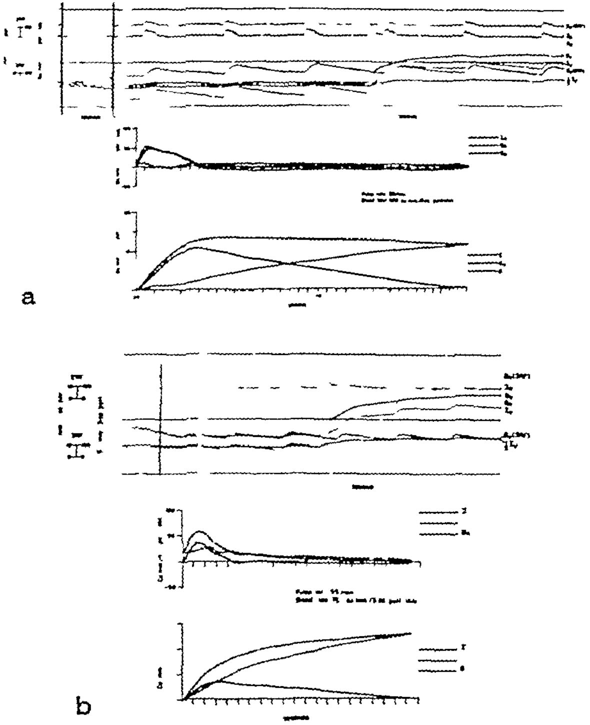


Fig. 7. Digital RPG of 63-year-old white man with complete heart block (Group A) before (a) and after (b) implantation of a cardiac electrode pacemaker. Consult text for details.

dyspnea even at rest. Furthermore all of the patients in Group A had angina pectoris.

Of the patients in Group B, 3 were completely asymptomatic and 4 had minimal symptoms including easy fatigability and exertional dyspnea. No patient had Adams-Stokes attacks. One patient had mild angina pectoris and exertional dysp-

ness and paroxysmal nocturnal dyspnea for which she was digitalized. This patient was studied by us twice within a 6 year period (1954 and 1960). The rheoplethysmogram showed little change during that time. The well developed alpha and beta deflections in patients of Group B, as well as the fact that blood continued to accumulate in the finger tip during diastole, indicate that the digital vessels were "loose" and that digital tone and, therefore, venous tone were not so high in Group B as in Group A. Since the patients in Group B were relatively asymptomatic, it is assumed that the myocardium was healthy enough to produce a stroke volume which was sufficient to compensate for the decrease in pulse rate.

It is concluded that in some patients with complete heart block there is a disproportionate degree of precapillary and postcapillary constriction. The relatively greater amount of postcapillary constriction was reflected by early "overfilling" of the venous reservoirs and leveling off of the I_1 curve. Since 80 per cent of the total volume of blood is contained within the venous system, venous constriction would be more effective than arterial constriction in maintaining cardiac output. In fact, arterial constriction would serve more to produce ischemia than to maintain cardiac output. Also, there is evidence that the baroreceptors in the aortic arch exert control over the peripheral blood vessels. If this is so, the low cardiac output may activate these receptors to increase venomotor tone.

Summary

The digital circulation in patients with complete heart block falls into two well defined patterns. In one group of patients (Group A), the digital venous system is "tight," so that relatively little blood flows into the digit during systole and no blood flows into the digit during diastole. In the other group (Group B), the

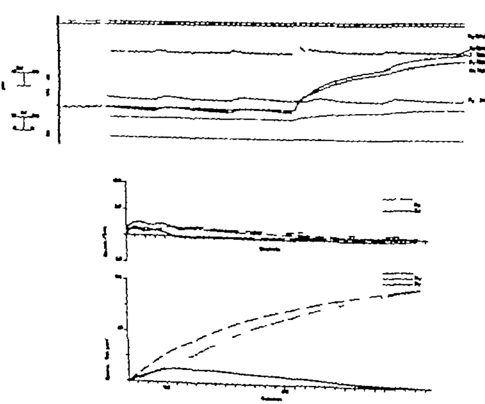
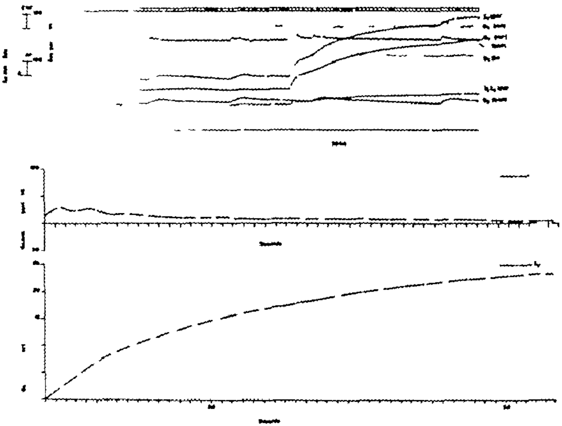


Fig. 8. Digital RLG of 59 year-old Negro man with ... heart block and a heart rate of 40 beats per minute. Consult text for details.



Digital RTC [illegible] during the compensatory pause after premature ventricular beat for the same patient whose [illegible] shown in Fig. 8. Note the continuous filling of the collecting vessels throughout the compensatory pause.

digital venous system is relatively "loose" so that blood flows into the digit during both systole and diastole. In the latter type the volume of inflow during systole may be so great that the collecting vessels become overdistended and the curve of inflow volume "levels off" during diastole. The two patterns described for the digital circulation in patients with complete heart block mirrored the clinical state. Patients in Group A were symptomatic, whereas those in Group B were essentially asymptomatic. Although a few patients in Group B complained of shortness of breath on exertion and one patient had angina pectoris, no patient in Group B suffered from Adams-Stokes attacks.

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Electrocardiographic recording of diaphragmatic action potential

*Stavros J. Deliyiannis, M.D.**
*Ibrahim A. Salama, M.D.***
Paramus, N. J.

It has been noticed that the depolarization of the diaphragm under certain circumstances can cause the registration of characteristic complexes on a technically good electrocardiogram.[1,4]

This electrocardiographic finding is very rare and generally has been attributed to abnormal involuntary contractions of the diaphragm. There have been numerous reports of abnormal diaphragmatic contractions of high or low frequency, but in very few cases have characteristic complexes been found in the electrocardiogram.[1,4]

The cases showing high frequency diaphragmatic activity have been divided into two main groups: (1) Diaphragmatic contractions displaying[2,3,4,11] the rhythm and the rate of the heart, probably due to the anatomic proximity of the phrenic nerves to the heart. Stimulation of these nerves by the electrical current produced by the depolarization of the ventricles may be responsible for the high frequency diaphragmatic activity.[8,11] As early as 1842 Carlo Matteucci produced contraction of one frog muscle by laying the nerve of this muscle across another contracting muscle.[1] It seems that increased excitability of the phrenic nerves is necessary for this type of abnormal diaphragmatic contraction because hypocalcemia and alkalosis or clinically evident tetany were present in all reported cases.[2,3,4,11] Electrocardiograms exhibiting diaphragmatic complexes synchronous with the heart rate have been reported by Soderstrom.[2,3] (2) Diaphragmatic flutter or tic with rates ranging from 35 to 380 and an average rate of 150 per minute.[12] In the majority of cases in which the rate of diaphragmatic contractions exceeded the heart rate the condition was considered to be a sequel of encephalitis.[12] Other etiological factors have included irritating processes along the phrenic path or of the diaphragm itself or psychogenic disturbances.[12]

In a recent review of diaphragmatic flutter[12] the electrocardiograms were normal in most cases. In a few cases there were alterations of the S-T segments and T wave during the paroxysms, but no diaphragmatic complexes were recorded.

Low frequency involuntary diaphragmatic contractions such as those which occur in singultus[4,8] have also been reported to cause electrocardiographic alterations. Their occurrence is less frequent than one would expect considering the common occurrence of singultus. In some cases hyperirritability of the phrenic nerves was postulated due to alkalosis or hypocalcemia.[8]

Soderstrom has described the diaphrag

From the Cardio-Pulmonary Laboratory, Bergen Pines County Hospital, Paramus, N. J.
Received for publication May 18, 1964.
*Formerly Fellow in Cardiology, Bergen Pines County Hospital, Paramus, N. J. Present address: [illegible], Greece.
**Fellow in Cardiology, Bergen Pines County Hospital, Paramus, N. J.

matic complex in the electrocardiogram as consisting of an initial short group of rapid oscillations (the myogram), which is followed by a shallow depression (the mechanogram). He considered that the myogram possibly represented the action potential of the cross-striated diaphragmatic muscles, and he attributed the mechanogram to the transmitted mechanical vibrations of the diaphragm. The diaphragmatic complexes are clearly registered only in the frontal plane leads, but are absent in Lead I[3,4] and less clearly visible in the precordial leads.

It is common experience that ordinary diaphragmatic activity, i.e., normal respiration, does not produce any electrocardiographic alteration of the nature described. Unsuccessful attempts were made to induce recording of the diaphragmatic complexes by deep or forced breathing or during maximal attempt at holding the breath.[1,3] Myograms were obtained only at the end of forced breathing or when the respiration was seriously embarrassed by artificial stenosis of the air passages.

The following case is presented because some interesting observations were made with regard to the diaphragmatic complexes.

Case report

This 9 year-old white man was hospitalized in November 1963 because of a throbbing headache, dizziness, vomiting, and epistaxis during the week prior to admission.

He had been hospitalized in June 1963 for myocardial infarction. He was conscious, coherent, afebrile, with a respiratory rate of 30 per minute. The breathing was not deep or labored. Moist rales were present over the left lung. No cardiomegaly or murmurs were detected. The pulse was irregular, with a rate of 88 per minute. No epigastric vibrations were noticed.

A chest x-ray film showed a dense irregular clouding of the major portion of the left lung. The hospital course was short and characterized by headache, restlessness, fever, cough, and epistaxis. He lapsed into coma a few days after admission. Respiration was rapid, with a rate of 35 per minute, quiet, and not assisted by auxiliary muscles. The patient died 7 days after admission in spite of the administration of massive doses of antibiotics. The main findings at autopsy were bronchopneumonia, old anteroseptal myocardial infarction, and generalized arteriosclerosis.

The laboratory data are presented in Table I. Of particular interest are several electrocardiograms taken during the final hospitalization. In Fig. 1 the rhythm is atrial fibrillation with an average ventricular rate of 100 per minute. There is digitalis effect and an old anteroseptal myocardial infarction. The diaphragmatic complexes of Soderstrom are clearly demonstrated in Leads II, III, and aVF, but are less obvious in Leads aVR and aVL and the precordial leads. They are absent in Lead I. These complexes occur regularly at a rate of 35 per minute. They are not related to the ventricular complexes. During the recording of the tracing it was documented that the beginning of the complex coincided with the onset of inspiration. This is shown in Fig. 2, where one observer indicated on the ECG tracing the beginning of inspiration. The horizontal bars coincided with the mechanogram of the complex.

Comments

Clinically, the patient was hyperventilating, which probably caused respiratory alkalosis.[1] This is in accord with the past experience that alkalosis, hypocalcemia, or tetany caused hyperirritability of the phrenic nerves and was invariably present in cases exhibiting diaphragmatic complexes. Unfortunately, no determination of serum calcium was made in this case.

This case differs from previous experience[3,4] in that the biphasic P wave-like mechanogram occurs first and the high-frequency myogram follows. We are unable to explain why there is inversion of the sequence of the two components of the diaphragmatic complex. The first component, which is of low frequency, is probably not a part of the action potential of the diaphragm, whose contractions are tetanic and therefore of high frequency, resembling somatic muscle tremor in the electrocardiogram.[3]

It is possible that the initial P wave-like deflection is an artifact due to deformation

Table I. Laboratory findings

Hemoglobin 12, Hematocrit 38 per cent
WBC 14,300. Differential: neutrophils 78 per cent, metamyelocytes 4 per cent, lymphocytes 14 per cent, monocytes 4 per cent
Sedimentation rate: 36 mm. in 1 hour
Prothrombin time 18.1 second. Control 15.4 second
Urinalysis: normal
SGOT 17, LDH 560
Fasting blood sugar 81. Blood urea nitrogen 6
Serum electrolytes: CO_2 19.2 mEq., Na 140 mEq., K 5.1 mEq., Cl 110 mEq.

Notice the low val[illegible] of CO_2 and high [illegible] of the chlorides [illegible] characteristic of respiratory alkalosis. Th[illegible] [illegible] blood [illegible] tre[illegible] [illegible]

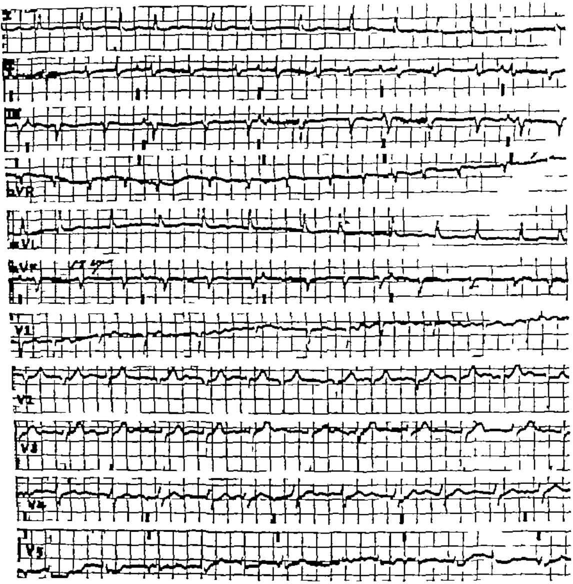


Fig 1 The diaphragmatic complexes occur regularly nd independent of the entricular complexes The low frequency mechanogram occurs first and followed by the h gh frequency m ogram The complexes are best recorded in the frontal plane leads but are absent in Limb Lead I and the right precordial lead The mechanogram i designated by small ertical bars



Fig The beginning of the horizontal bars at the bottom of the tracing mark the onset of the pir tion hich o ncides precisely with the mechanogram The latter is designated by heavy dots

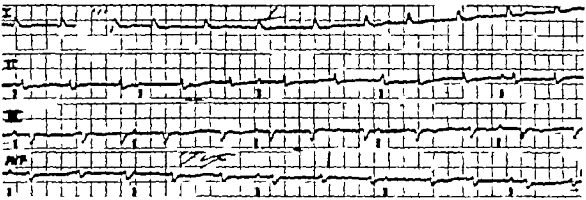


Fig. 3. The high frequency myogram is not clearly recorded in the limb leads. The regularly occurring mechanogram (designated by small vertical bars) could give the erroneous impression of atrial dissociation with uniatrial fibrillation.

potentials of the skin arising as a result of varying electrode pressure on the skin during inspiration.[3,4] However, this cannot explain the higher amplitude of this deflection in the frontal plane leads because the respiratory chest excursions should effect changes mainly in the local potentials underneath the precordial electrodes. This mechanism could explain certain published tracings which demonstrated large deflections of the base line in the precordial leads of hiccuping patients.[5] However, no myograms are visible in these tracings.

The distribution of the diaphragmatic complexes in the limb leads might be due to a particular orientation of the responsible vectorial forces—electrical, mechanical, or combined—which lie in the frontal plane perpendicular to Lead I and also more or less perpendicular to the plane of the precordial leads. The shape and symmetry of the diaphragm, its anatomic position, and the direction of its respiratory movements could account for this particular orientation of the electromechanical diaphragmatic vector.

Electrocardiographic records exhibiting diaphragmatic complexes are indeed rare. This finding was noticed only once in more than 18,000 electrocardiograms obtained during the past 3 years in this laboratory. It seems that respiratory alkalosis or hypocalcemia does not always produce this finding, which could depend on the severity of the biochemical disturbance as well. In tracings with less obvious myograms, the P wave-like and regularly occurring mechanogram could give the erroneous impression of atrial dissociation[24] with or without uniatrial fibrillation. This diagnosis was entertained on the basis of the initial tracings from our patient (Fig. 3) before the case was further investigated by observation of the patient's respiration while the tracings were being recorded.

Summary

The registration of diaphragmatic complexes in the electrocardiogram of a hyperventilating patient is described in which an inversion of the sequence of myogram and mechanogram was noticed. The possibility that an electromechanical diaphragmatic vector parallel to the frontal plane was responsible for the large amplitude of the complexes in some of the standard leads is discussed. Finally, the rarity of this electrocardiographic finding is stressed and the possibility of its being misinterpreted as indicating atrial dissociation is mentioned.

We wish to express our appreciation to Dr. Joseph Grayzel, Director of the Cardiopulmonary Laboratory, Bergen Pines County Hospital, for review of this paper and helpful recommendations.

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Antagonism of the contractile effect of digitalis by EDTA in the normal human ventricle

*Sidney Cohen, M.D.**
Arnold M. Weissler, M.D.
Clyde D. Schoenfeld, M.D.
Columbus, Ohio

Studies on animals and isolated hearts have demonstrated diminished contractile activity and reduced effectiveness of cardiac glycosides when ionized calcium is decreased.[1-4] Although the effectiveness of lowering serum calcium in abolishing digitalis-induced arrhythmias is clinically established,[5] the effect of a decrease in serum calcium on the positive inotropism of digitalis in man has not been demonstrated.

The increase in myocardial systolic force that follows digitalis has previously been shown[1,6] to be associated with shortening of the ejection phase of mechanical systole. Recent studies[7] have demonstrated a similar and dose-dependent decrease in left ventricular ejection time after digitalis in the normal human ventricle. Therefore, *the left ventricular ejection time may be* employed as a means of assaying the contractile effect of digitalis. In the present study, the effect of laboratory-induced hypocalcemia on the ejection time response to deslanoside was investigated.

Methods

All subjects were normal male university students who ranged in age from 20 to 27 years. The studies were begun in the morning after overnight fasting, and all observations were made with the subject supine and in a basal state. On each individual, control determinations of heart rate, left ventricular ejection time, and serum electrolytes were made for 30 to 60 minutes prior to any drug administration, and serial determinations were continued at appropriate intervals during the study. Venous blood for determination of electrolytes was withdrawn from an indwelling Cournand needle which was inserted during the control period. Left ventricular ejection time was determined from external pulse tracings obtained from a funnel-shaped device placed on the skin over the point of maximal impulse of the carotid artery. The carotid arterial pulse wave was amplified by a Statham P23Db transducer and recorded at a paper speed of 100 mm. per second, with time markers at 0.02 second

From the Department of Medicine, The Ohio State University Health Center, Columbus, Oh[illegible].
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*Present address: [illegible] East [illegible] Road, C[illegible], Oh[illegible] [illegible]

intervals A Standard Lead II electrocardiogram and a phonocardiogram were recorded simultaneously as reference tracings The left ventricular ejection time was measured from the beginning of the upstroke to the incisural notch and determined by averaging 10 consecutive complexes Heart rate was calculated from the average R R interval of these complexes Ejection time was corrected for heart rate as described previously [8] according to the equation

$$ETI = LVET + .0016\ HR$$

where ETI is ejection time index LVET is left ventricular ejection time and HR is heart rate A change in the ejection time index may reflect either alterations in the slope of the normal regression equation relating heart rate and left ventricular ejection time or the magnitude of left ventricular ejection time or both

Ionizable calcium was determined by titration with Na_2 EDTA using Cal Red as the indicator as described by Bachra Dauer and Sobel [9] Total calcium was determined by flame spectrophotometry Magnesium was determined by the method of Orange and Rhein [10] Sodium and potassium were determined by flame photometry with the aid of an autoanalyzer

In 12 subjects the response to deslanoside 1.6 mg intravenously was studied for 8 hours after its administration Two hours after deslanoside had been administered a placebo infusion consisting of 250 ml of 5 per cent dextrose in water or normal saline solution was given intravenously over 30 minutes

In repeat studies on 9 of the above mentioned subjects an identical protocol was followed except that Na_2 EDTA 3 Gm was added to the intravenous infusion which was begun 2 hours after the administration of deslanoside

In 4 additional subjects deslanoside was followed at 2 hours by an infusion containing Ca EDTA 3 Gm intravenously administered over a 30 minute interval Nine additional subjects received Na_2 EDTA 3 Gm intravenously without prior digitalization and in these individuals the effects of Na_2 EDTA alone were followed for 6 hours

[illegible]

Statistical analysis was performed according to the methods of Snedecor [11]

Results

The effects of deslanoside followed by placebo infusion are summarized in Table I In these control studies on 12 subjects the administration of deslanoside was attended by a prompt decrease in the ejection time index which averaged 16 msec ($p < .001$) below control levels at 2 hours The intravenous infusion at 2 hours had no effect on the ejection time index and the digitalis induced shortening persisted for 8 hours The decreased ejection time index was accompanied by a relative bradycardia during the first 6 hours after administration of the drug and was unaffected by the placebo infusion Serum ionizable calcium did not change during this study Serum potassium rose slightly but consistently immediately after deslanoside No significant alterations in other serum electrolytes were noted throughout the period of observation (see Appendix)

The alterations induced by Na_2 EDTA on the deslanoside response are summarized in Table II and Fig 1 In the 9 subjects who received Na_2 EDTA 2 hours after deslanoside the infusion was followed by an increase in heart rate and a

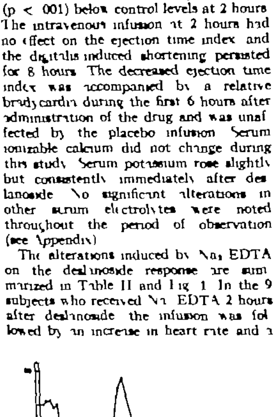


Fig 1 The effects of deslanoside (1.6 mg intravenously) followed by Na_2 EDTA (3 Gm intravenously) on the ejection time index and serum ionizable calcium in 9 subjects

Table I Effects of deslanoside (1 6 mg I V) in normal subjects

Subject		Before deslanoside						Minutes after deslanoside		
		1	2	3	4	5	6	10	20	40
R C	HR	59	59	58	59	59	59	53	53	50
	ETI	411	411	409	412	411	411	403	400	399
	Ca	—	—	9 3	9 6	9 3	9 4	9 3	9 6	9 6
J L	HR	61	59	60	60	58	60	5?	53	51
	ETI	399	39?	399	398	395	398	381	380	384
	Ca^{++}	—	—	9 0	9 0	9 3	9 1	9 3	9 3	9 6
J E	HR	72	77	71	75	76	74	65	65	?0
	ETI	395	40?	399	404	404	401	381	380	39?
	Ca^{++}	—	—	10 0	10 0	10 0	10 0	9 6	10 0	10 3
A K	HR	68	69	67	67	69	68	56	51	5?
	ETI	416	411	412	407	413	41?	383	384	391
	Ca^{++}	—	—	9 6	9 3	9 6	9 5	9 6	10 0	9 6
J K	HR	63	64	58	56	57	60	54	60	56
	ETI	399	393	401	394	393	397	390	386	335
	Ca^{++}	—	—	9 7	10 0	10 0	9 9	—	—	9 7
J K	HR	59	53	59	59	60	58	55	53	60
	ETI	401	392	397	391	396	395	381	381	376
	Ca	—	—	9 6	9 6	10 0	9 7	9 6	9 6	10 0
P M	HR	50	47	47	44	46	47	45	50	47
	ETI	413	405	409	403	407	408	397	400	40?
	Ca^{++}	—	—	10 0	9 3	9 6	9 6	9 6	10 0	10 0
R M	HR	69	67	63	65	55	64	49	49	5?
	ETI	406	408	406	408	395	405	388	385	390
	Ca	—	—	9 3	9 6	9 6	9 5	9 3	9 0	9 6
L O	HR	65	65	64	65	61	65	60	58	60
	ETI	405	405	407	400	409	405	392	391	385
	Ca	—	—	9 6	9 6	9 3	9 5	9 3	9 3	9 3
B P	HR	60	61	62	60	60	61	6?	63	66
	ETI	417	413	416	416	419	416	405	400	406
	Ca	—	—	10 3	10 6	10 3	10 4	10 3	10 6	10 9
R P	HR	72	73	69	68	69	70	59	59	53
	ETI	410	415	409	410	412	411	395	391	393
	Ca^{++}	—	—	9 3	9 3	9 3	9 3	9 6	9 3	9 6
R R	HR	44	44	45	47	50	46	41	39	40
	ETI	418	420	419	414	418	418	400	398	402
	Ca^{++}	—	—	10 0	10 0	10 0	10 0	10 0	10 6	10 6
Av	HR	6?	6?	60	60	61	61	54	54	55
	ETI	407	407	407	404	406	406	391	390	39?
	Ca^{++}	—	—	9 6	9 7	9 7	9 7	9 6	9 8	9 9

HR Heart rate ETI Ejection time index (msec) Ca Serum [illegible] (in mgram per cent)

Minutes after deslanoside											
60	90	120	130	140	150	180	210	240	300	360	480
48 407 9 6	48 400 9 6	46 397 9 6	47 396 9 6	49 396 9 6	48 397 9 6	50 390 9 3	47 392 9 6	50 390 9 6	49 387 9 6	55 384 10 0	54 381 10 3
51 379 9 6	51 381 10 0	50 378 10 3	51 380 10 3	52 381 10 3	50 379 10 3	50 375 10 6	53 373 10 6	52 374 10 6	64 385 10 3	58 387 10 0	60 382 10 0
66 393 10 3	64 387 10 3	63 386 10 0	77 394 10 3	77 397 10 3	69 398 10 0	81 400 10 6	74 398 10 6	78 403 10 3	67 391 10 3	65 387 10 0	72 378 9 6
57 387 9 6	50 386 10 0	53 389 9 6	51 385 9 6	57 393 9 6	56 390 9 6	59 391 10 0	59 386 10 0	59 386 9 3	58 397 9 6	66 385 9 6	63 380 9 6
47 385 10 0	48 381 10 3	53 383 10 6	46 375 10 3	49 380 10 6	47 381 10 3	59 376 10 3	53 373 —	57 379 10 0	60 373 10 3	58 370 10 6	54 374 —
64 383 10 0	56 378 10 0	50 378 10 0	47 377 10 3	53 379 10 0	48 380 10 0	58 371 10 0	57 375 10 3	60 373 9 3	56 384 9 3	66 363 9 6	59 369 10 9
51 401 10 0	50 394 9 3	44 390 10 6	45 391 10 6	53 403 10 6	49 395 10 9	52 388 10 3	57 378 10 3	56 387 10 0	50 389 10 3	56 401 10 9	58 384 10 3
52 387 9 3	48 384 9 6	57 390 9 3	53 393 9 6	50 397 9 6	48 387 9 3	49 379 9 3	50 391 9 6	50 386 9 6	49 392 10 0	55 389 10 0	54 387 10 3
60 393 9 6	61 381 9 6	60 384 10 0	63 386 9 6	67 388 9 3	63 386 9 6	62 377 9 6	61 380 9 6	63 381 9 6	61 386 9 3	68 381 9 6	7 389 10 0
64 403 10 6	60 399 10 6	56 399 10 3	70 409 10 3	68 407 10 6	53 403 10 3	67 385 10 3	69 393 10 6	72 395 10 3	— — —	73 388 10 0	85 397 10 3
60 403 10 0	67 397 10 0	56 407 10 3	5 398 10 3	56 398 10 3	50 400 10 3	49 390 10 6	59 390 10 3	56 398 10 3	58 399 9 6	78 396 9 6	83 387 10 0
37 395 10 9	39 405 10 6	38 403 10 9	44 408 10 9	38 406 10 6	35 405 10 3	44 399 10 0	43 401 10 3	42 397 10 3	39 397 10 3	43 400 10 3	50 402 10 3
55 393 10 0	54 389 10 0	57 390 10 1	53 391 10 1	55 393 10 1	57 392 10 0	5 393 10 1	57 386 10 2	58 387 9 9	56 389 9 9	62 386 10 0	64 393 10 1

Table II Effects of deslanoside (1.6 mg I.V.) and Na_2 EDTA (3 Gm I.V.) in normal subjects

Subject		Before deslanoside						Minutes after deslanoside		
		1	*2*	*3*	*4*	*5*	*6*	*10*	*20*	*40*
P C	HR	48	48	46	50	51	49	44	42	45
	ETI	420	416	417	413	413	416	406	404	403
	Ca^{++}	—	—	10.0	10.0	9.6	9.9	9.6	10.0	10.0
J E	HR	64	66	70	69	67	67	60	58	58
	ETI	395	399	401	400	399	399	387	385	391
	Ca	—	—	9.6	10.0	10.0	9.9	10.0	10.0	10.3
A K	HR	71	68	69	65	77	70	59	64	58
	ETI	426	425	427	426	432	427	409	411	409
	Ca^{++}	—	—	9.0	8.7	—	8.9	8.7	9.0	9.0
J K	HR	58	59	58	61	61	59	57	57	56
	ETI	395	396	402	407	393	398	382	386	384
	Ca	—	—	10.0	9.6	9.6	9.7	9.3	9.6	10.0
I M	HR	51	51	51	51	50	51	47	46	45
	ETI	417	419	417	417	413	417	407	409	406
	Ca	—	—	—	9.4	9.4	9.4	—	—	9.4
R M	HR	56	55	59	59	54	56	42	43	47
	ETI	407	407	402	408	404	406	383	383	392
	Ca	—	—	—	9.4	9.7	9.6	—	—	—
L O	HR	63	62	63	63	63	63	61	62	66
	ETI	403	403	406	403	403	404	393	388	397
	Ca	—	—	9.3	9.3	9.6	9.4	10.0	9.6	10.0
P I	HR	66	70	70	70	61	67	58	57	61
	ETI	412	417	414	413	408	413	390	386	391
	Ca^{++}	—	—	10.0	10.0	9.6	9.9	10.0	10.3	10.0
R R	HR	66	59	56	56	57	59	45	43	42
	ETI	413	408	411	412	415	412	390	392	398
	Ca^{++}	—	—	9.6	10.0	9.6	9.7	10.0	10.0	10.0
X	HR	60	60	60	60	60	60	53	53	53
	ETI	410	410	411	411	409	410	394	394	396
	Ca^{++}	—	—	9.6	9.6	9.6	9.6	9.7	9.8	9.8

HR Heart rate *ETI* Ejection time index (msec) *Ca^{++}* Serum ionizable calcium (milligrams per cent)

prompt and consistent prolongation of the ejection time index. The prolongation in the ejection time index completely reversed the digitalis-induced shortening and actually lengthened the ejection time index over the control level. The Na_2EDTA induced changes were significant ($p < .01$) when compared to the original deslanoside response. The alterations in the ejection time index after deslanoside and Na_2 EDTA were associated with no significant change in the slope of the fundamental regression relationship relating heart rate and left ventricular ejection time. During the infusion the mean serum ionizable calcium fell from 9.7 to 7.1 mg per cent ($p < .01$). The Na_2 EDTA effect on the ejection time persisted from 40 to 60 minutes and reflected the changes in ionizable calcium. As the ionizable calcium approached control levels the digitalis-induced shortening of the ejection time index and the relative bradycardia reappeared and persisted for the remainder of the study. No significant

Minutes after deslanoside											
60	*90*	*120*	*130*	*140*	*150*	*180*	*210*	*240*	*300*	*360*	*480*
45 404 9 6	45 399 10 0	43 398 10 0	48 406 9 3	56 419 7 5	68 421 6 5	50 408 7 5	49 406 7 8	50 407 8 4	63 409 8 4	54 394 8 7	52 385 9 3
58 390 10 0	59 393 10 0	56 391 10 3	63 402 9 6	87 422 8 7	90 427 7 5	76 409 8 1	66 396 8 4	65 396 8 1	69 397 8 7	65 395 9 0	58 381 9 0
64 407 9 0	66 399 9 0	54 395 8 7	70 422 8 4	99 440 7 1	100 440 5 8	76 419 6 5	70 412 7 1	60 404 7 5	68 404 7 8	68 401 7 8	64 383 8 1
58 380 10 0	56 384 10 0	66 392 9 6	63 407 9 6	72 408 8 4	88 409 7 1	77 387 8 1	61 379 8 4	59 385 8 4	57 371 8 7	72 3 4 9 0	64 381 9 0
48 406 9 4	47 406 —	49 406 10 0	54 413 8 4	59 423 8 1	67 429 7 5	52 406 8 1	53 402 8 4	55 405 8 7	64 40 8 4	79 396 9 1	63 400 9 4
46 390 9 4	50 387 9 7	54 388 9 7	55 399 9 7	66 403 8 6	77 412 8 2	57 395 8 0	57 391 7 8	50 386 8 2	58 384 8 6	56 383 8 6	49 382 9 0
68 394 10 0	70 395 10 3	65 390 10 3	69 389 9 3	85 395 —	97 407 7 1	80 390 7 8	78 389 8 1	69 391 8 4	79 390 8 7	81 385 8 7	71 384 8 7
71 394 10 0	72 395 10 3	57 387 10 0	74 415 8 4	80 416 7 5	80 409 7 1	76 387 7 8	93 396 8 1	62 391 8 1	69 404 8 4	79 395 8 7	78 404 8 7
41 399 10 0	41 396 9 6	41 393 10 0	47 403 9 3	61 407 8 4	62 411 7 5	53 404 7 8	46 394 8 1	43 405 8 4	44 396 8 7	43 397 9 0	47 390 9 3
55 395 9 7	56 395 9 9	54 393 9 8	61 406 9 1	73 415 8 0	81 418 7 1	66 401 7 7	64 396 8 0	57 396 8 7	63 395 8 5	66 391 8 7	61 388 8 9

alterations in serum sodium potassium magnesium or total calcium were induced by the Na_2 EDTA infusion (see Appendix)

The infusion of Ca EDTA after deslanoside in 4 subjects produced no changes in the ejection time index heart rate or serum ionizable calcium (Table III) Hence the effect of Na_2 EDTA was mediated through its ability to bind ionizable calcium specifically

The ejection time response to Na_2 EDTA in 9 undigitalized subjects was similar to that in the digitalized subjects but differed in magnitude (Table IV Fig 2) The magnitudes of the EDTA induced changes in the digitalized and the undigitalized groups were compared by superimposing the postinfusion curves (Fig 3) The prolongation of the ejection time index after Na_2 EDTA was significantly greater in the digitalized subjects ($p < 01$) and approached twice that of the undigitalized subjects These differences in response to Na_2 EDTA occurred at a time when the

Table III Effects of deslanoside (1 6 mg I V) and Ca EDTA (3 Gm I V) in normal subjects

Subject		Befor deslanoside						Minutes after deslanoside		
		1	*2*	*3*	*4*	*5*	*Av*	*10*	*20*	*40*
R C	HR	61	55	58	57	58	58	49	51	5?
	ETI	408	409	416	411	412	411	407	400	399
	C	—	—	10 0	9 6	9 6	9 7	9 6	10 0	10 3
I H	HR	70	73	7?	74	71	72	63	63	57
	ETI	384	389	391	394	396	391	377	369	366
	Ca	—	—	10 0	10 0	10 0	10 0	10 0	10 0	10 0
I H	HR	57	58	53	53	53	55	48	48	45
	ETI	409	408	406	405	409	40	394	393	394
	Ca^{++}	—	—	9 3	9 6	9 6	9 5	9 6	10 0	9 6
R M	HR	70	6	53	54	51	58	45	46	46
	ETI	413	409	408	413	404	409	389	389	386
	Ca	—	—	9 3	9 3	9 6	9 4	9 6	9 3	9 3
Av	HR	65	6?	59	60	59	61	51	52	51
	ETI	404	404	405	406	405	405	39?	388	386
	Ca	—	—	9 7	9 6	9 7	9 7	9 7	9 8	9 8

HR Heart rate *ETI* E t ime index (msec) C % ion izable calcium (milligrams per cent)

changes in ionizable calcium were of the same magnitude in the two groups

Discussion

In light of previous observations that alterations in calcium ion concentration have a profound effect on the response of isolated heart muscle to cardiac glycosides[1, 5, 18] it seemed pertinent to investigate this phenomenon in man It is especially desirable that the response to digitalis be compared over the range of calcium concentrations commonly encountered clinically

The dose dependent shortening of the ejection time in response to digitalis[7] furnishes a convenient means of assaying digitalis action under varying conditions The present study has demonstrated that Na EDTA in normal subjects antagonized the contractile effects of digitalis as manifested by the reversal of the digitalis induced shortening of the ejection time index It is notable that neither deslanoside nor Na₂ EDTA induced significant alteration from the normal regression coefficient Hence the changes observed in the ejection

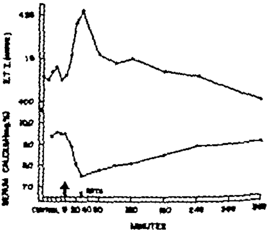


Fig 2 The effects of Na EDTA (3 Gm intravenously) on the ejection time index and on serum ionizable calcium in 9 subjects

time index reflect directly a change in magnitude of the duration of left ventricular ejection The degree of prolongation of the ejection time index paralleled the decrease in serum ionizable calcium When the serum ionizable calcium returned to

Minutes after dedicated											
60	*90*	*120*	*130*	*140*	*150*	*180*	*210*	*240*	*300*	*360*	*480*
47 398 10 0	48 398 10 0	47 394 10 0	51 398 10 0	48 399 9 3	48 401 9 6	46 389 10 0	48 386 10 0	47 390 9 6	46 389 9 6	— 399 10 0	52 384 10 3
59 363 10 0	57 366 10 3	57 368 10 3	52 367 10 0	54 371 9 6	53 370 9 6	53 362 10 0	50 363 10 0	53 363 10 0	49 367 10 3	67 377 10 3	60 361 10 0
51 395 10 0	48 392 9 6	49 386 9 6	49 385 9 6	50 390 9 6	50 393 9 3	46 383 9 3	45 382 9 6	49 385 9 6	48 386 9 6	47 379 10 0	48 380 10 3
46 387 11 2	49 391 10 6	48 39 10 9	49 395 10 6	51 399 10 0	49 396 9 6	48 395 9 6	47 383 9 6	47 379 10 0	65 386 10 0	64 373 9 6	52 377 9 3
51 386 10 3	51 387 10 1	49 385 10	50 376 10 1	51 390 9 6	50 390 9 5	48 387 9 7	48 379 9 8	49 379 9 8	57 38 9 9	59 387 10 0	53 376 10 0

ward control levels the digitalis effect again became apparent

The failure of Ca EDTA to alter the ejection time in digitalized subjects and the absence of significant alterations in total serum sodium potassium and magnesium after the infusion of Na EDTA would indicate that it is indeed the reduction in ionizable calcium that is responsible for the antagonism of the digitalis response

The prolongation of ejection time with Na$_2$ EDTA in the undigitalized subjects is consistent with earlier observations in animals that myocardial contractility is diminished by decreased levels of calcium ions[17,19] However the prolongation of the ejection time index in the digitalized subjects approached twice that in the undigitalized subjects although the changes in ionizable calcium were identical in the two groups This would imply that the response of the digitalized ventricle to Na$_2$ EDTA induced hypocalcemia represents antagonism rather than the simple addition of opposing effects

It is of importance to note that the duration of left ventricular ejection in normal individuals not only is dependent upon heart rate but relates directly with stroke volume and hence cardiac output

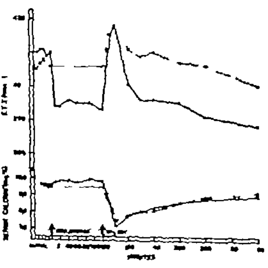


Fig 3 Comparison of the effects of Na EDTA (3 Gm intravenously) in digitalized subjects (*solid line*) and undigitalized subjects (*dashed line*) Dotted line connects control values with the infusion period in the undigitalized group.

Table IV Effects of Na EDTA (3 Gm IV) in normal subjects

Subject		Before EDTA					
		1	*2*	*3*	*4*	*5*	*6*
N N	HR	65	67	65	63	63	65
	ETI	397	407	393	403	407	400
	Ca	—	—	9 1	9 4	—	9 3
C B	HR	61	57	55	56	51	56
	ETI	413	411	412	411	410	411
	C	—	—	10 0	10 0	9 6	9 9
E D	HR	69	65	68	68	63	67
	ETI	409	408	413	409	411	410
	Ca	—	—	9 3	9 3	9 3	9 3
I H	HR	73	73	73	72	67	71
	ETI	424	425	430	431	419	425
	C	—	—	10 3	10 3	10 6	10 4
D M	HR	57	57	51	52	53	53
	ETI	397	393	391	393	399	393
	Ca	—	—	9 1	9 4	9 4	9 3
I M	HR	51	51	54	52	48	5
	ETI	390	386	393	391	388	390
	Ca⁺	—	—	9 4	9 7	9 7	9 6
R M	HR	57	58	57	56	54	57
	ETI	393	396	400	397	393	397
	Ca	—	—	8 8	9 1	8 8	8 9
J R	HR	58	57	56	62	58	58
	ETI	421	425	431	428	419	425
	Ca^{++}	—	—	9 1	9 4	9 4	9 3
C S	HR	69	68	67	67	67	68
	ETI	407	402	401	410	411	406
	Ca^{++}	—	—	9 3	9 6	9 3	9 4
Av	HR	62	61	61	61	59	61
	ETI	406	405	407	408	405	406
	Ca^{++}	—	—	9 4	9 6	9 5	9 5

HR Heart rate *ETI* Ejection time index (msec) *C* Serum [illegible] ble calcium (in Mg per cent)

The administration of digitalis results in an abbreviation of left ventricular ejection time in the absence of a change in cardiac output manifesting the enhanced rate of left ventricular ejection Preliminary studies indicate that the antagonism of digitalis effect by Na_2 EDTA is similarly unassociated with significant alteration in cardiac output

As noted previously[7] deslanoside induced a consistent slowing of heart rate that was reversed by the infusion of Na_2 EDTA Although Na_2 EDTA alone induced an increase in heart rate in undigitalized subjects this chronotropic effect was of greater magnitude in the digitalized subjects

The results of the present study then would indicate that Na_2 EDTA induced hypocalcemia antagonized both the inotropic and chronotropic effects of digitalis in the normal human ventricle Finally

Minutes after EDTA								
10	20	30	60	90	1 0	150	240	360
64 406 9 1	? 418 8	7? 41? 7 4	7 411 4	71 393 7 9	0 394 6	64 40 8 5	68 409 8 8	6 40 9 4
68 420 8 4	6 435 7 3	85 437 6 2	77 471 7 5	66 417 7 8	69 418 7 8	60 413 8 4	59 415 8 1	67 403 8 4
71 416 8	80 476 7 8	90 433 6 8	78 423 7 5	66 417 8 1	73 470 8 1	65 471 8 4	4 416 9 0	1 398 9 0
71 415 9 6	86 430 8 7	93 436 8 1	87 4 1 8 4	90 474 8 1	82 4 8 8 7	6 478 9 0	? 41 9 6	4 419 9 3
55 394 8 5	6 401 7 6	68 404 7 4	60 394 7 9	55 391 8 2	55 39 8 5	55 398 5	55 393 9 1	69 390 9
57 388 9 7	54 39 9 4	54 391 8 8	61 390 7 9	53 38 7 9	5 39 7 9	5 38 8 5	50 389 8 8	65 43 9 4
63 406 8 8	63 40 8 5	63 409 8 5	 409 7 6	65 410 9	67 401 6	8 38 8 7	8 393 8	51 389 8 5
80 433 8 8	? 479 8 7	81 433 7 9	68 47 8 7	63 477 8	6 474 8 5	60 4 2 9 1	64 419 9 4	69 413 9 4
73 470 8 1	78 4 7 1	79 47 6 8	69 409 7 8	64 416 8 1	61 416 8 1	61 403 8 4	66 40 9 0	68 39 8
66 411 8 9	71 418 8 1	6 4 1 5	77 411 8	66 409 8 0	65 410 8 1	61 40 8 5	63 406 8 9	68 400 9 1

the present study illustrates the application of the left ventricular ejection time as a convenient and simple means of following changes in ventricular contractility.

Summary

1 The administration of deslanoside to normal subjects is associated with a highly significant shortening of the ejection time index.

2 The reduction in serum ionizable calcium induced by the administration of Na EDTA to digitalized subjects is attended by a prompt and consistent reversal of the digitalis induced shortening of the ejection time index.

3 The administration of Na EDTA in undigitalized subjects evoked significantly less prolongation of the ejection time index than in digitalized individuals although the changes in serum calcium were identical.

4 It is postulated that a reduction in

Appendix

	Before deslanoside				*Minutes after deslanoside*				
	1	*2*	*3*	*Av*	*10*	*20*	*40*	*60*	*90*
Deslanoside (1 6 mg I V)—Average of 12 Subjects									
Ionizable Ca	9 6	9 7	9 7	9 7	9 6	9 8	9 9	10 0	10 0
Total Ca			9 8			9 9		10 0	
Potassium	4 2	4 3	4 3	4 2	4 4	4 6	4 7	4 8	4 7
Sodium	140	141	141	141	141	143	143	144	144
Magnesium	2 4	2 4	2 4	2 4	2 4	2 5	2 5	2 5	2 5
Deslanoside (1 6 mg I V) and Na EDTA (3 Gm I V)—Average of 9 Subjects									
Ionizable Ca	9 6	9 6	9 6	9 6	9 7	9 8	9 8	9 7	9 9
Total Ca			9 9			10 0		10 0	
Potassium	4 0	4 ?	4 1	4 1	4 3	4 5	4 6	4 6	4 7
Sodium	143	143	143	143	143	145	146	145	143
Magnesium	2 5	2 4	2 4	2 4	2 5	2 5	2 4	? 3	2 5
Deslanoside (1 6 mg I V) and Ca EDTA (3 Gm I V)—Average of 4 Subjects									
Ionizable Ca	9	9 6	9 7	9 7	9 7	9 8	9 8	10 3	10 1
Total Ca			9 4					9 6	

Na EDTA (3 Gm I V)—Average of 9 Subjects

	Before EDTA				*Minutes after EDTA*	
	1	*2*	*3*	*Av*	*10*	*20*
Ionizable Ca	9 4	9 6	9 5	9 5	8 9	8 1
Total Ca			9 9		10 1	
Potassium	4 2	4 2	4 3	4 2	4 3	4 3
Sodium	14?	140	140	140	141	140
Magnesium	2 ?	2 3	2 2	2 ?	2 3	? 3

Comparison of Effects of Deslanoside and Deslanoside + Na_2 EDTA

	1	*2*	*3*	*4*	*5*	*Av*	*Minutes*			
							10	*20*	*40*	*60*
ETI	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Serum Ca	—	—	NS	NS	NS	NS	NS	NS	NS	NS

ionizable serum calcium antagonizes the contractile effects of deslanoside as reflected by these alterations in the ejection time index

We wish to express our appreciation to Mrs Susan Eriksen Mrs Virginia Schafer Mrs Lois Scoles and Miss Mary Tart for their able technical assistance

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Minutes after deslanoside									
120	*130*	*140*	*150*	*180*	*210*	*240*	*300*	*360*	*420*
10 1	10 1	10 1	10 0	10 1	10 2	9 9	9 9	10 0	10 1
10 0			10 0	10 0	10 0	10 0			10 0
4 8	4 9	4 7	4 7	4 7	4 6	4 4	4 3	4 4	4 2
146	149	147	149	147	146	144	143	143	144
2 5	2 4	4	2 5	5	2 5	2 4	2 5	2 4	4
9 8	9 1	8 0	7 1	7 7	8 0	8 2	8 5	8 7	8 9
9 9			9 8	9 8	9 8	9 9			9 7
4	4	4	4 5	4 3	4 3	4 4	4 4	4 1	4 2
145	145	145	144	145	145	145	146	144	144
2 5	2 4	2 4	2 4	4	2 4	2 3	2 4	2 3	2 4
10 2	10 1	9 6	9 5	9 7	9 8	9 8	9 9	10 0	10 0
9 8			9 6	9 7	9 7	9 7			10 1

Minutes after EDTA						
30	*60*	*90*	*1 0*	*180*	*240*	*360*
7 5	8	8 0	8 1	8 5	8 9	9 1
9	9 9	9 7	9 9			10 0
4 3	4 2	4 2	4 1	4 2	4 3	4 1
140	141	143	140	144	147	141
2	2	3	2	2 1		2 5

Minutes										
90	*1 0*	*130*	*140*	*150*	*180*	*210*	*40*	*300*	*360*	*420*
NS	NS	< 01	< 01	< 01	< 01	< 05	< 05	NS	NS	NS
NS	NS	NS	< 05	< 01	< 01	< 01	< 05	< 05	< 05	< 05

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The exercise electrocardiogram

Experience in analysis of "noisy" cardiograms with a small computer

*Pentti Rautaharju, M.D., Ph.D.**
Halifax, N. S., Canada
*Henry Blackburn, M.D.***
Minneapolis, Minn.

An extraordinary burden on electrocardiographic technique is imposed by requirements of cardiovascular epidemiological studies involved in comparisons of heart disease rates, establishing levels of work tolerance, and assessing therapeutic and preventive measures. Quantitative comparison is the essence of these studies. For ECG measurement and analysis, human or machine, excellent quality records with improved ratio of the ECG signal to the record "noise" are a necessity.[1]

This report considers the possibilities realized and the limitations encountered in certain techniques which extract the ECG with the aid of a small computer from noisy records made during performance of heavy work.

Instrumentation and computing method

The method described is the average response computing technique modified for analysis of transient, not strictly periodic functions, and here called *average transient computing* (ATC). The technique is an old one, and the theory is simple, but application to biologic measurements is recent[2] (principally electroencephalographic studies of evoked responses). The computing instrument is a small portable special purpose computer of average transients (the CAT†) which converts the analog form of the physiologic signal to simple (digital) numbers, stores these in its memory, and manipulates them to provide averages over a prescribed number of heartbeats.

The system is diagrammed in figure 1. FM radiotelemetry of the ECG is not essential, and although it simplifies both the work test procedure and recording on magnetic tape, it introduces problems of distortion in the frequency range of primary interest.[1] However, the anticipation and triggering process is crucial to the method and makes use of a delay provided by the distance between ordinary record and playback heads of the tape recorder. An arbitrary but unambiguous portion of the R wave is "read" by the record head to provide a timing pulse or trigger. This instructs the computer to start sampling data as it arrives at the playback head from the same heartbeat trigger and at the

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*Department of Physiology and Biophysics, Dalhousie University, Halifax, Nova Scotia, Canada.
**Laboratory of Physiological Hygiene, University of Minnesota School of Public Health, [illegible], Minneapolis, Minn. [illegible]
†Mnemotron Division, Technical Measurement Corporation, North Haven, C[illegible]

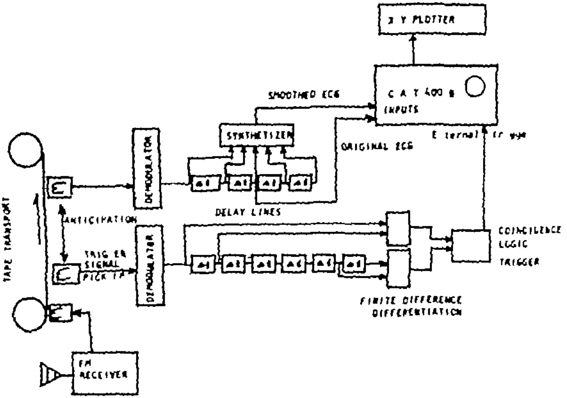


Fig. 1. System block diagram for average transient computing, smoothing, and coincidence logic triggering.

same phase of the ECG irrespective of beat to beat variations in R-R interval. A version without anticipation is adequate if the interest is only in analysis of the S-T segment of the ECG or of functions associated with mechanical events of the cardiac cycle.

The rate of the sampling process and the time over which samples are taken for each heartbeat are determined beforehand and programmed by knobs on the face of the computer. The analysis time can be selected within a range from 31 milliseconds to 15 seconds. The number of addresses or analysis points available is 400. This means that if an analysis time of 0.5 second is selected, samples of ECG amplitudes will be taken at intervals of 1.25 milliseconds.

When the sampling process has been initiated by the R wave trigger, each sample number is stored in the corresponding address number in the computer memory. A value proportional to the amplitude of the analog signal at a certain sampling point is added to that sampled and stored from the same sampling point of the previous cardiac cycle. The total sampling process is repeated from successive cardiac cycles until the number of ECG complexes desired, set by the pulse counter, is summed.



Fig. 2. Above: A noisy ECG record from a bipolar chest lead of a patient taken during moderately heavy treadmill exercise. Below: A read-out of the smoothed complex representing an average of 16 beats.

Those components of the record which occur in an erratic (random) way unrelated to the timing reference tend when added algebraically to cancel each other This eliminates most of the random noise in ECG tracings associated with variations in skin-electrode contact and impedance and muscle potentials during physical exercise While the random components tend to cancel the components which occur regularly and are locked in phase to the trigger impulse are reinforcing themselves The result is an increase in the ratio of the signal to noise which can be shown to be proportional to the square root of the number of heartbeats summed This process applied to 100 beats taken during effort would result in 10 times less noise in relation to the ECG signal The averaged signal is displayed on the oscilloscope screen of the computer by touching a panel button or is written out on a direct writer an x-y plotter a printer or a computer typewriter or punched on paper tape for input to general purpose digital computers

Results

Fig 2 shows at the top a record of a bipolar chest lead typical of that obtained *during* heavy treadmill work in a middle aged man without cardiovascular symptoms but identified as having S-T change by his postexercise electrocardiogram Interpretation only of heart rate or gross arrhythmia is possible to the physician monitoring such a record on a direct writer or on an oscilloscope The figure below is an average of only 16 heart cycles written out on an x-y plotter It is cleaned up enough to be clinically interpretable

Fig 3 shows an average QRST from the standing control record in the same individual with the S-T portion of the averaged response *during* effort superimposed The time scale of the records in Fig 3 has been normalized so that the duration of the S-T is the same in the control and exercise records The S-T change during exercise is adequately displayed for measurement or empirical interpretation

The ATC method has been used not only to reduce the noise of electrocardiographic signals but to eliminate the respiratory interference in other signals and to isolate the respiratory component for study using a trigger signal derived from a respiratory function Noise reduction has been accomplished as well in the impedance plethysmogram and the ultralow frequency ballistocardiogram

Discussion

The average transient computing method shows promise for the processing of noisy exercise electrocardiograms and has proved to be feasible in the analysis of records made in other difficult conditions associated with noise such as thermal stress experiments [8] However the importance of routine noise reduction by proper grounding careful skin electrode contact preparation use of special electrodes etc before recording the ECG cannot be overemphasized Any method employed for noise reduction *afterward* results in some degradation of the signal

Proper use of average transient computing requires knowledge and management of errors inherent in the process which include smoothing and blurring errors and errors due to artefacts

Smoothing and smoothing error The record processed with average transient computing such as is shown in Fig 3 is adequately free of noise for most clinical applications However closer examination of such a record amplified reveals residual

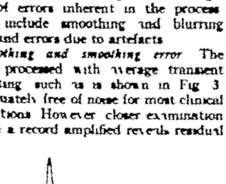


Fig 3 The averaged S-T segment during exercise is superimposed its time scale expanded on the averaged standing control record in the same individual as in Fig 2

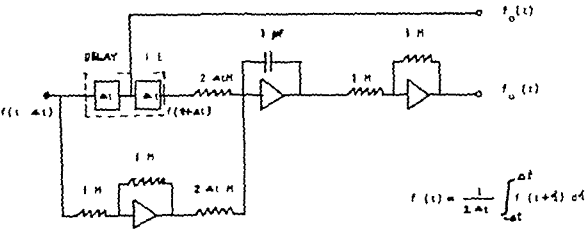


Fig. 4. Circuit diagram of an electronic moving average filter.

noise which requires further reduction for computer programs of automatic wave form recognition. This residual noise can be reduced by sampling a larger number of ECG complexes, but in the case of transient phenomena, such as S-T depression in exercise, a long time period of data accumulation is not desirable. Algebraic summation also cancels transient changes of physiologic interest. For this reason, as well as to reduce chances of encountering artefacts, the time a signal is averaged should be the shortest possible.

Residual noise can be effectively reduced by statistical filtering, i.e., smoothing with moving average or moving parabolic fit programs. Smoothing is an operation in which each sampled value of the ECG amplitude is replaced by a weighted combination of the values at several adjacent sampling points, thus reducing the effect of random variation at any one data point. A large scale digital computer is neither necessary nor economical for smoothing and an analog system developed for this purpose is illustrated in Fig. 4, the diagram of an electronic *moving average* filter. Fig. 5 illustrates the results of its application in S-T segment analysis.

Although intentional smoothing as a well-defined operation is necessary in automated data processing, unintentional smoothing may significantly distort the signal without the investigator's awareness. When ordinary amplitude triggering is used for average transient computing, a distortion of the averaged signal occurs which we call *smoothing error*. For example, when an amplitude threshold of the R wave is used for triggering, samples do not always enter the same computer address but are scattered among several adjacent addresses because of inevitable fluctuations of the record base line. The extent and the characteristics of unintentional smoothing with amplitude triggering can be indirectly inferred with the aid of dwell time histogram techniques using the CAT computer. The dwell time is the

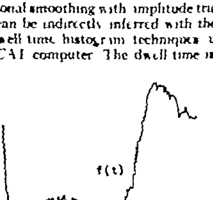


Fig. 5. Amplified S-T segment of an averaged exercise ECG smoothed with the moving average filter of Fig. 4.

time interval that a signal such as the R wave exceeds a predetermined amplitude threshold and a histogram of dwell times is shown in Fig 6 computed from an experiment using an R amplitude threshold of 0 6 mV The curve above the histogram is the cumulative or probability distribution function From this function it is estimated that 68 per cent of the dwell times are within ±2 5 milliseconds of the median Ignoring possible variations in the shape and the duration of the R wave one can assume as an approximation that variations in the dwell time are mainly caused by beat to beat base line fluctuations Since the intervals between sampling points are here 1 25 milliseconds amplitudes sampled from a large number of ECG complexes with respect to a fiducial point on each R wave are scattered among several adjacent computer addresses and with a distribution that approaches a normal distribution

The effect of smoothing error is distortion of the higher frequency components of the signal a rounding of the peaks The extent to which this distortion takes place may not be critical for analyses of slowly changing segments such as the S T segment but is significant in many other situations

Smoothing error of this sort may be avoided by base line restorer circuitry and by utilizing slopes rather than amplitudes for triggering The derivative is frequently employed but again its successful use requires smoothing and/or filtering to avoid erratic triggering by noise

Blurring error Amplitude measurements are in themselves averages over a finite time interval The precision of a D C amplitude measurement from a signal superimposed on noise tends to improve with the square root of the time interval over which the measurement is averaged but a *blurring error* occurs if the signal does not remain constant over the sampling interval This type of error is not unique to average transient computing [14]

Nonrandom noise and other artefacts In the elimination of noise from cardiographic signals caused by respiratory action it is assumed that the respiratory components (noise) and the cardiac components (signal) are random with respect to each other i e that the amplitude of one at any instant can in no way be predicted from knowledge of the other This is not strictly so since the heart frequency is modulated by the inspiratory and the expiratory movements It can happen that more ECG complexes are sampled during inspiration than during expiration which results in a biased average

If artefacts such as extrasystoles or sudden D C shifts due to loose electrode contacts are summed with the regular ECG components averages may be produced that do not correspond to any real cardiac signal These artefacts can be obviated to a large extent by coincidence logic triggering methods To eliminate extrasystoles or to selectively pick up extrasystoles a triggering circuit has been employed in the system depicted in Fig 1 which triggers only if there is a rising signal with a slope exceeding a threshold followed at a predetermined time interval

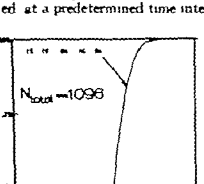


Fig 6 The dwell time histogram gives the distribution of time interval during which 1098 successive R waves exceeded an amplitude threshold of 0 6 mV The curve above the corresponding probability distribution which provides an estimate of the magnitude of smoothing error occurring in average computing methods

by a negative slope exceeding another threshold

Finally averages obtained by average transient computing such as the "cleaned up" ECG are in themselves a limited statistic Other principles must be employed to obtain information on variations in the (ECG) signal or characteristics of the noise And from the analytical standpoint averages represent only a beginning

Summary

Experience in the development and application of a method for extracting cardiographic signals from noisy records is reported The method here called *average transient computing* (ATC) is based on modifications of well known average response computing techniques ECG complexes of several successive cardiac cycles are coherently summed so that random noise in the record tends to cancel itself and the ratio of the ECG signal to the noise improves in proportion to the square root of the number of beats summed The result is a "cleaned up" ECG suitable for clinical interpretation or quantitative measurement

Proper use of the increasingly available small devices for average transient computing requires knowledge and management of errors inherent in the process Sophisticated triggering methods with anticipation and delay techniques are necessary to avoid averaged records which have little relevance to the original cardiographic function A coincidence logic pattern triggering method is described for the prevention of distortion of the averaged signal by artefacts such as extrasystoles and intentional smoothing of the ECG is carried out with electronic analog systems

It is emphasized that the averaged record obtained by this computing method is a limited statistic that serves as a starting point for empirical interpretation or for more detailed quantitative analysis of information contained in the exercise electrocardiogram

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Serotonin induced pulmonary venous spasm demonstrated by selective pulmonary phlebography

*Brent M. Parker, M.D.**
*Barry W. Steiger, M.D.***
Martin J. Friedenberg, M.D.
St. Louis, Mo.

Until recently, the pulmonary veins were regarded merely as passive channels through which blood flowed to the left atrium. They now are known to develop pathologic changes associated with chronic pulmonary venous hypertension or increased pulmonary blood flow.[1] Complex catheter studies in open-chest dogs have furnished evidence which suggests that the pulmonary veins play a dynamic role in the circulation of the lung.[2,3] The present study was undertaken in an attempt to elucidate further the vasomotor activity of pulmonary veins by means of selective phlebography. Serotonin was used to investigate pulmonary venomotion because it has been shown to increase the pulmonary vein–left atrial pressure gradient.[2]

Method

The technique and normal findings in selective pulmonary phlebography have been described in detail in another report. Sixteen mongrel dogs were lightly anesthetized with intravenously administered sodium pentobarbital (27 mg. per kilogram). An end-hole catheter was introduced into a common carotid artery through a small arteriotomy and passed retrograde through the ascending aorta, left ventricle, and left atrium into a pulmonary vein. The tip of the catheter was positioned 2 to 3 cm. dorsal to the posterior border of the left atrium. Other catheters were passed into the right ventricle and the femoral artery for the recording of pressure with Statham strain-gauge transducers.

For angiography, 15 ml. of 50 per cent sodium diatrizoate† was injected with a Cordis automatic injector‡ in order to deliver the bolus of contrast material within 1 or 2 seconds. Films were exposed at a rate of 2 or 3 per second for 5 seconds in the lateral projection. The beginning of the injection of contrast material was timed to coincide with the end of expiration.

At least one preliminary control pulmonary phlebogram was obtained in each animal. Five to 30 minutes later, 100 to 300 micrograms of serotonin creatine phosphate per kilogram of body weight was

From the Department of Medicine and The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo.

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*Address: Department of Medicine, Washington University School of Medicine, [illegible] St. Louis, Mo. [illegible]
**Postdoctoral Fellow [illegible] U. S. Public Health Service.

†Hypaque, Winthrop Laboratories, New York, N. Y.
‡The Cordis Company, Miami, Fla.

injected into the pulmonary artery or right ventricle. Pulmonary phlebography was repeated 15 to 30 seconds later at the peak of the rise in pulmonary arterial pressure induced by the serotonin using precisely the same injection and roentgenographic technique as in the control injection. Thus each animal served as its own control.

Additional control angiograms were obtained on seven occasions 5 to 60 minutes after the original examination in order to ascertain whether the control phlebograms were consistent after more than one injection of contrast material. As control observations in 2 dogs phlebograms were obtained before and immediately after 150 ml. of normal saline had been infused into the pulmonary artery. In 4 other animals pulmonary artery angiography was performed before and after the administration of serotonin in order to investigate pulmonary arterial vasomotor reactivity to serotonin.

In 5 dogs arterial oxygen saturation was determined by cuvette oximetry before and after the administration of serotonin. Alterations in cardiac output were studied in 5 dogs after injection of serotonin and in 3 animals after infusion of 150 ml. of normal saline using the dye-dilution method of Gabe, Fuckman and Shillingford.[4]

Results

Satisfactory phlebograms before and after the administration of serotonin were obtained in 8 of the 16 dogs studied. Twelve examinations were performed in these 8 animals. In 5 of the examinations serotonin induced distinct changes in the appearance of the vessels indicating pulmonary venous contraction. These alterations consisted of narrowing of peripheral veins, kinking and abrupt tapering of medium sized veins (Fig. 1) and dilatation of central veins. In addition, serotonin caused a marked reduction in retrograde filling of the pulmonary veins in all 12 examinations (Figs. 1 and 2). The small venous radicles which were well filled in the control films were poorly filled after serotonin. Serotonin also reduced significantly the amount of capillary blush (Figs. 1 and 2) and retrograde filling of the pulmonary arteries (Fig. 1).

In most experiments contrast material entered the left atrium and aorta more rapidly after serotonin than in control animals, probably reflecting the fact that retrograde filling was reduced.

The examinations were unsatisfactory in 3 dogs because the catheter was positioned too far from or too close to the left atrium, because the injection rate was too slow, or because a multiple side hole catheter was used which flooded the field with contrast material.

The serotonin caused a twofold to fourfold increase in pulmonary arterial pressure in each animal and often a slight rise in systemic pressure. It also induced tachypnea, micturition and defecation. Cardiac output increased an average of 45 per cent after serotonin and 38 per cent after 150 ml. of normal saline. In most animals arterial oxygen saturation was not changed appreciably by serotonin.

In the 7 dogs in which repeat control phlebograms were obtained with or without infusion of saline no difference between the first, second and third control examinations could be detected. Repeat phlebograms after infusion of saline were not different from the control studies. These observations established that the angiographic changes after serotonin were not merely the result of a prior injection of contrast material, an elapse of time or an increase in cardiac output.

Contraction of a pulmonary vein at its junction with the left atrium was not observed in these experiments. This area, however, was often incompletely filled.

Pulmonary arteriography before and after serotonin showed that serotonin caused dilatation of the larger pulmonary arteries, narrowing of peripheral arteries and a reduction in capillary filling (Fig. 3). In 3 of the 4 studies kinking of the medium sized arteries and abrupt tapering of these arteries at their major divisions were observed. The contrast material also arrived in the left atrium earlier. These pulmonary arterial changes are similar to those described by Hirschman and Boucek.[6]

Discussion

There is increasing evidence that the pulmonary veins contract under certain circumstances. The data which support

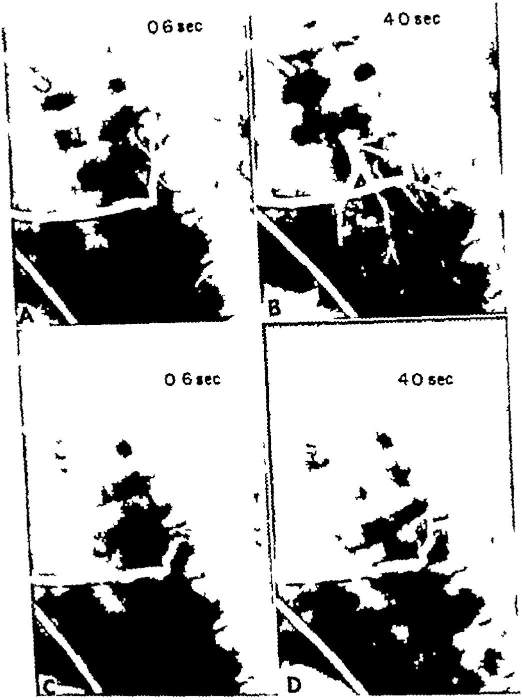


Fig. 1. A and B: Control selective pulmonary phlebograms. A normal arborizing pattern of pulmonary venous tree is noted in A with marked capillary filling and arterial reflux in B. C and D: Selective pulmonary phlebograms after serotonin in the same animal, using identical injection and roentgenographic techniques. Kinking and abrupt tapering of the opacified medium-sized veins are seen, as well as marked reduction in retrograde filling of peripheral pulmonary veins, capillaries and arteries.

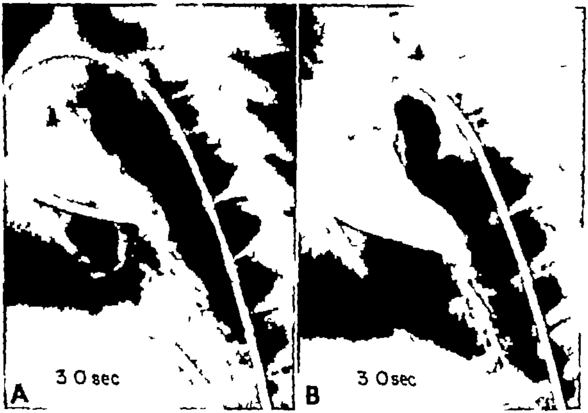


Fig. 1. A, Control selective pulmonary phlebogram showing normal opacification of peripheral veins and capillaries. B, Selective pulmonary phlebogram after serotonin in the same animal using identical technical and roentgenographic factors. Narrowing of peripheral veins and a marked decrease in opacification of peripheral veins and capillaries are demonstrated.

pulmonary venomotion may be grouped into six categories.

1. Anatomic study of the pulmonary veins. Pulmonary veins larger than 80 micra in diameter usually contain an irregular circular layer of smooth muscle and abundant autonomic nerve fibers and ganglion cells. The histologic appearance of the veins suggests that they are capable of motor activity.[12] In man the striated muscle of the left atrium overlaps by 10 mm. the smooth muscle of the walls of the pulmonary veins.[8] The atrial muscle forms a sleeve of myocardium which encloses the proximal portion of the pulmonary veins. The location and appearance of this sleeve of muscle suggests that it might have a sphincter-like action.

2. Muscular hypertrophy of the pulmonary veins in response to pulmonary venous hypertension. The development of musculoelastic hypertrophy in the pulmonary veins of dogs with aortic–left atrial anastomoses[9] and in dogs and man with pulmonary venous hypertension[13] supports the concept that the pulmonary veins play an active role in disease conditions. Such hypertrophy could be the result of unusually intense or sustained venomotion.

3. Contraction of isolated pulmonary veins in vitro. In 1911 Campbell[14] found that epinephrine elicited slight constriction of the isolated pulmonary veins of sheep. Later Franklin[7] showed that epinephrine contracted the pulmonary veins of dogs. In 1951 Smith and Coxe[11] studied isolated pulmonary veins from man, dog, and swine. They measured changes in volume of perfused segments in response to drugs. Epinephrine, histamine, and acetylcholine constricted the pulmonary veins of dogs, and epinephrine and histamine constricted the pulmonary veins of man. Spirally cut segments of pulmonary veins from dogs also have been shown to contract slightly in response to serotonin.[15]

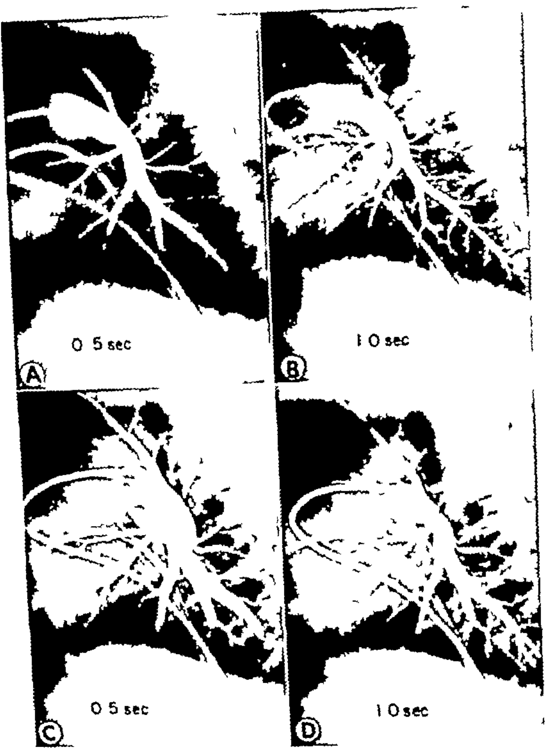


Fig. 3. A and B. Control pulmonary arteriogram showing normal arborizing pattern of pulmonary arteries. C and D. Pulmonary arteriogram after serotonin in the same animal using identical injection and roentgenographic techniques. Dilatation of larger arteries, narrowing of peripheral arteries and reduction in capillary filling are shown. Kinking of medium sized arteries and abrupt tapering of these arteries at their major divisions are present.

4. Presence of high-altitude pulmonary edema in man when left atrial pressure is normal. Fred and associates[13] reported the case of a patient with high-altitude pulmonary edema in whom the left atrial pressure was 9.3 mm. Hg and pulmonary arterial pressure was 68/39 mm. Hg. The presence of pulmonary edema suggested that the increase in resistance was not in the pulmonary arterioles but in the pulmonary veins. However, on the basis of normal pulmonary arterial wedge pressure in 4 such patients, the authors of a recent study concluded that pulmonary venous constriction was not present.[14]

5. Development of an increased pressure gradient between the pulmonary veins and the left atrium as a result of anoxia or drug administration. Bean and associates[15] postulated that the decrease in cardiac output and increase in lung volume caused by elevation of the level of carbon dioxide in the blood were evidence of pulmonary venoconstriction. Eliakim and associates[16] showed that 20 per cent saline administered intravenously led to an increase in pulmonary arterial, pulmonary venous, and pulmonary arterial wedge pressures, whereas the left atrial pressure was unchanged. This effect was thought to be due to spasm at the pulmonary vein–left atrial junction. Others, however, were unable to confirm these findings and postulated that the elevation of pulmonary arterial pressure was due to agglutination of red blood cells in the capillaries.[17] Eliakim and co-workers repeated their own studies and concluded that the sphincter effect was observed only in the veins of the upper and middle lobes, which vessels they found had more abundant musculature.[18]

Pulmonary venous constriction in the dog has been reported after the administration of gram-negative endotoxin,[19] histamine, serotonin, and epinephrine.[20] Hypoxia also causes an increase in the pulmonary vein–left atrial pressure gradient,[21] but pulmonary embolism does not. Eliakim and Aviado,[22] utilizing constant perfusion in open-chest dogs, showed an increased resistance in pulmonary venous segments after the stimulation of sympathetic nerves and after the administration of epinephrine, acetylcholine, serotonin, histamine, and angiotensin. Rudolph[3] has obtained similar results in dogs after the injection of serotonin or after the creation of an aortic-pulmonic shunt, but he found that acetylcholine abolished the gradient. He was not able to determine the site of venous constriction.

Although most of the above-mentioned studies suggest that the pulmonary veins may constrict, some of the drawbacks in these studies should be mentioned. A number of problems are involved in the measurement of pressures through a catheter in a pulmonary vein. The size of the catheter is of major importance. Gilbert and associates[9] used a catheter with an outside diameter of 1.2 mm. and found that pulmonary venous pressures varied considerably from lung to lung and from one placement to another, depending on the distance the catheter was inserted into the vein. If the catheter was wedged into a pulmonary vein, the pressure increased as compared to that in the pulmonary artery. Sudden increments in pulmonary venous pressure, equaling pulmonary arterial pressure, occasionally occurred after drug administration and were attributed to closure of the vein around the catheter, resulting in a wedge venous pressure. Aviado used catheters with an outside diameter of 1.0 mm. and 0.4 mm. The pressure recorded through the larger wedged catheter was approximately equal to pulmonary arterial pressure, whereas a lower pressure was measured with the smaller catheter. The lesser pressure was thought to represent venular pressure. It is difficult to understand why wedging catheters of different sizes gives such different pressure readings. Fishman[14] has expressed concern about the validity of the pressures measured from pulmonary veins, since a good pressure pulse is not obtained.

Another problem in the interpretation of changes in pressure in pulmonary veins after drug administration is the relationship between pressure, flow, and resistance. Since pressure equals flow times resistance, an increase in pressure may represent an increase in flow without change in resistance. In some studies, controlled pulmonary perfusion has been used.[8,11,5,3] Under these circumstances of constant flow, changes in pressure reflect changes

in resistance Although this type of experimental model in open chest dogs will allow studies of the direct effects of drugs on the pulmonary venous resistance the circumstances are unphysiologic The pulmonary circulation is a low pressure system normally subject to changes in intrathoracic pressure Interruption of the nerve supply to the heart and lungs in the preparation of controlled perfusion models may alter vascular reflexes and the response to drugs The above mentioned limitations in the study of pressure gradients made it desirable to obtain confirmatory in vivo evidence of pulmonary venomotion

6 *Pulmonary venous angiography* Kjellberg and associates [9] studied the pulmonary veins in 6 dogs after injection of contrast material into the right ventricle or pulmonary artery They described constriction of the pulmonary veins at the left atrial–pulmonary vein junction and changes in the density of the contrast material which were consistent with venous constriction However the published illustrations have poor contrast density and the area in question is visualized poorly We are unable to detect venous constriction in their figures

The technique of selective pulmonary phlebography[4] makes it possible to demonstrate pulmonary venomotor activity without the difficulties in the measurement of pressure described above and with the subject in a more nearly physiologic state

The present study has provided the first in vivo graphic evidence of pulmonary venous constriction Kinking and abrupt tapering of medium sized veins and narrowing of peripheral veins were observed in nearly one half of the experiments after the administration of serotonin The absence of distinct changes in venous caliber in some of the animals may be explained by the fact that most studies were performed in the veins of the lower lobe in which there is some evidence that venomotion is less [1] In addition spasm of the relatively thin walled veins may have been overcome in some instances by the pressure and volume of the injection The relative lack of retrograde filling of the pulmonary veins and capillaries after serotonin may result from pulmonary venular constriction This concept is supported by the central venous distention and the rapid flow of contrast material into the left atrium and ventricle after serotonin Another possible explanation for the lack of retrograde flow is the increase in cardiac output after serotonin An increase in forward flow might prevent retrograde passage of contrast material and carry it forward more rapidly However it is unlikely that the lack of retrograde flow observed in our study was due to an increase in cardiac output after the administration of serotonin because serotonin causes relatively small increments in flow (15 16 or 20 per cent) [4,5] a finding we have confirmed Furthermore an injection of normal saline in a quantity sufficient to elevate the cardiac output as much as does serotonin caused no alteration from the control pattern

Our study does not provide information in regard to the question of a sphincter action at the left atrial–pulmonary vein junction [9,16] Although constriction in this region was not observed the definition of the area was often poor rendering accurate evaluation impossible The central dilatation of the pulmonary veins after serotonin might support the concept of a sphincter However the dilatation could also be explained by passive distention of the veins due to rapid injection of a large amount of contrast material with peripheral venous constriction preventing retrograde decompression

Summary

Selective pulmonary phlebography before and after infusion of serotonin has graphically demonstrated active in vivo pulmonary venomotion for the first time The evidence of venous constriction was of two types (1) decreased retrograde pulmonary venous capillary and arterial filling and (2) distinct changes in the caliber of the veins with kinking and narrowing

These findings add further weight to the accumulating evidence of other types which indicates that the pulmonary veins are not merely passive channels but serve an important hemodynamic function

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Determination of the external work and power of the left ventricle in intact man

*Robert E. Snell, M.D.**
*Peter C. Luchsinger, M.D.***
Washington, D. C.

The external work of the left ventricle in man is usually calculated from mean pressure volume measurements. Such estimates are deficient in at least two respects. First, some arithmetic error is introduced in determining the total work done, as demonstrated by Katz in 1932. Second, the use of mean data gives no information concerning the temporal pattern of work performance in a system in which pressure and flow are highly pulsatile.

The development of the computed pressure gradient technique by Fry and his associates[2] has made possible the measurement of instantaneous blood flow and velocity in the human ascending aorta. The use of this technique in conjunction with simultaneous determinations of instantaneous aortic pressure makes possible accurate computations of ventricular power and work in man[4] that avoid the above-mentioned deficiencies. The present study reports observations in individuals without known systemic cardiovascular disease as well as in patients with nonvalvular heart disease during a control state. In addition, a group of subjects have been studied during the administration of a pressor amine.

Method

A. Theory. Work represents the product of a force by the distance over which the force acts; power is the time rate at which work is done. In hydraulic systems, in which the force is usually measured as a pressure, the equivalent expressions for work and power involve the pressure-volume and pressure-volume flow products, respectively.

The external or "useful" work of the left ventricle is defined as the work required to maintain a pressure upon the volume of blood ejected into the ascending aorta and to impart a velocity to it.[3] Since the work done represents the temporal integral of the power provided to the flowing blood during the ejection period, external ventricular work may be computed from Equation (1) (*see top of page 530*).

*[illegible] Hospital, Washington, D. C., and [illegible] School of Medicine.

**[illegible] Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

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[illegible] School of Medicine. Address: [illegible] Hospital [illegible] Washington, D. C.

**[illegible] Hospital, Washington, D. C. [illegible] Professor of Medicine, Georgetown University School of Medicine.

$$LVSW = \left(\int_{t_0}^{t} PQdt + \int_{t}^{t_1} \frac{\rho Q^3}{2g} dt\right) 100 \qquad (1)$$

where LVSW = left ventricular stroke work (Gm.M. per beat), P = instantaneous aortic pressure (cm. H_2O), Q = instantaneous aortic blood flow (c.c./sec.), v = instantaneous aortic blood velocity (cm./sec.), ρ = density of blood (average 1.057 Gm./c.c.), g = gravitational constant (980 cm./sec.²), and t_0 to t_1 = systolic ejection period (sec.).

The first term of Equation (1) is generally called the "pressure" work, whereas the second represents the "kinetic," or "accelerative," work. This latter quantity represents the correction for the work done in moving the blood mass to the site of measurement in the ascending aorta.

In the absence of values for instantaneous velocity and flow, external ventricular work has been approximated by the mean pressure–stroke volume product:

$$\overline{LVSW} = \overline{P} \times \overline{SV} \qquad (2)$$

The accelerative term is generally ignored. If mean systolic pressure is used, results from Equation (2) will approximate those from Equation (1) with varying degrees of accuracy.[4] Other investigators[5] have used the difference between mean arterial pressure and left atrial or left ventricular end-diastolic pressure as the first term on the right in Equation (2).

B. Patient material. A total of 19 male patients from the Veterans Administration Hospital, Washington, D. C., were studied (Table I). Eleven (Group I) had no evidence of systemic cardiovascular disease. The other 8 had clinical findings suggestive of primary myocardial disease (Group II). In this hospital this diagnosis is applied to young adults who demonstrate cardiomegaly and symptoms and signs of low-output congestive heart failure in the absence of angina pectoris, persistent or significant hypertension, organic valvular disease, constrictive pericarditis, or evidence of systemic neuromuscular or metabolic disease. At the actual time of study only 1 patient was in congestive heart failure (J.A.C., No. 16); the other 7 had past histories of congestive failure, together with present evidence of cardiac enlargement and nonspecific electrocardiographic abnormalities.

Because of the variations in body size between and within the two groups, all values for work and power were expressed as indices in order to facilitate comparison. As indicated above, one individual had manifestations of overt cardiac failure at the time of study; accordingly, the expression of work in terms of body surface area in this subject may be falsely low because of the retention of fluid.

C. Experimental procedure. All patients were studied in the fasting state without premedication. Surgical exposure of the femoral artery was achieved under local anesthesia. A specially designed catheter* with two pairs of lateral openings separated by a distance of 5 cm. was introduced and advanced to the ascending aorta under fluoroscopic control just distal to the aortic valve. The final position of the catheter was documented by x-ray. Observations at rest were made over a period of approximately 30 minutes. Four subjects from Group I were also studied during the administration of l-norepinephrine† by intravenous infusion at a rate of 4 micrograms per minute.

1. PRESSURE MEASUREMENT. The catheter lumina were connected to two strain gauges‡ used in conjunction with chopper-stabilized low-level amplifiers.§ The system was tested prior to each study, using a pneumatic sine wave generator‖ to assure that dynamic imbalance was less than 5 per cent of the input pressures at 15 cycles per second and that the dynamic single-ended response was uniform (±5 per cent) over the same frequency range.

*U. S. Catheter and Instrument Company, Glens Falls, N. Y.
†Levophed, Winthrop Laboratories, New York, N. Y.
‡Model P23Db, Statham Transducers, Inc., Hato Rey, Puerto Rico.
§Model 350-1100, Sanborn Co., Waltham, Mass.
‖Nat. and Instrument Laboratories, Kensington, Md.

Phase lag was linear through 15 cycles per second and approximated 1 degree per cycle per second The static imbalance was less than 0 1 per cent over a pressure range of 300 cm H O These are the minimum requirements listed by Greenfield and Fry[8] for the measurement of aortic blood velocity by the computed pressure gradient technique

2 VELOCITY AND FLOW MEASUREMENT Instantaneous velocity measurements were made by the method described by Fry and his co workers[8] Barnett Greenfield and Fox[10] and Snell and associates[11] using a Donner analog computer A calibration of the instantaneous velocity tracing in terms of flow was obtained by first determining the mean velocity by planimetry Three to five consecutive cardiac cycles at the time of the determination of cardiac output by the dye dilution technique were used for this purpose The mean height of the velocity curve was then set equal to the mean flow obtained by the dye-dilution technique resulting in a flow calibration of the velocity tracing

In the four studies employing l nor epinephrine dye curves were repeated

Table I Physical characteristics of patients studied

Patient (Number)	Age (yr)	BSA (M²)
Group I No cardiovascular disease		
H L B (10)	41	1 70
A I (13)	33	1 90
J A (26)	37	1 67
W H P (7)	36	1 86
J Mc (30)	42	1 66
J W B (12)	43	1 99
W A H (11)	40	1 5
B W (19)	31	1 56
C A (18)	44	1 72
R L F (9)	47	1 57
I C (29)	37	1 99
Group II Myocardial disease		
F S (5)	44	1 89
M J (24)	37	1 76
H S I (22)	36	1 95
J W C (17)	44	2 05
H M (21)	40	1 5
R M C (20)	34	2 18
J A C (16)	49	1 90
J M (23)	47	1 60

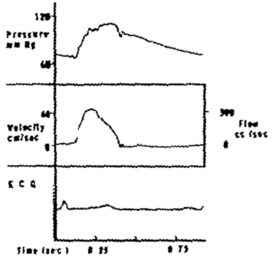


Fig 1 Recordings of pressure and velocity (flow) obtained in the ascending aorta of a subject without cardiovascular disease (J Mc No 30)

during administration of the drug and the calibration procedure was repeated In all instances this second calibration agreed within 5 per cent with that obtained during the control period

This method of flow calibration neglects changes in radius during the cardiac cycle which normally approximate 5 per cent in the ascending aorta It also assumes that flow in the ascending aorta becomes zero at end-diastole as demonstrated by Spencer and Denison[1]

Cardiac outputs were determined by the dye-dilution technique using a cuvette densitometer* and a fixed speed withdrawal pump† Duplicate measurements of cardiac output made with this technique are reproducible to ±5 per cent in this laboratory

3 WORK COMPUTATION Representative pressure and velocity (flow) curves obtained in one individual are shown in Fig 1 Measurements for work computation commenced with the initial upstroke of the pressure wave and terminated at the incisura Tracings were obtained at a paper speed of 100 mm per second and ordinate values were determined at 0 01 second intervals Computations of work from Equation (1) were accomplished

*Model 302-EK G Reed Instruments Laboratories Inc Oberl Ohio
†Harvard Instrument Co Dover Mass

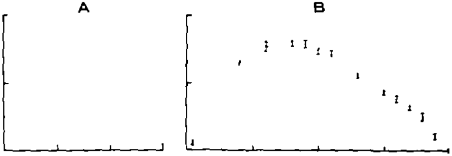


Fig. 2. A: Ventricular external power output as a function of time in a subject from Group I (VI No. 13). B: The temporal pattern of work performance in the subjects of Group I. The individual points represent average values for instantaneous power obtained in 11 individuals and the vertical lines define the standard error of the mean. The basis has been nondimensionalized and expressed as per cent duration systolic ejection.

using digital computation with card punch input.* Average stroke work values were also obtained from Equation (2) using values for mean systolic pressure and mean flow obtained by computer integration of the area under the curves.

Results

Table II lists the mean values for heart rate, aortic pressure, cardiac index, and stroke and minute work indices in the individuals without cardiovascular disease (Group I). In 2 of these subjects (R. L. No. 9 and L. C. No. 29) the resting heart rate was above 100 during repeated measurements. Since no cause for this sinus tachycardia was evident other than anxiety, they were retained in the control group.

The resting stroke work index ranged from 51 to 90 Gm. M./M.² per beat, with the lowest values being found in the patients with rapid heart rates. The kinetic fraction of the total work was small, never exceeding 3 per cent of the total work output. Even at peak ejection that fraction of instantaneous power related to the accelerative force never exceeded 5 per cent.

Fig. 2 A shows a typical representation of the temporal pattern of work performance obtained in one of the subjects in Group I. The illustration represents an average of five separate pressure and flow curves recorded at rest. To obtain a composite power curve for the 11 subjects the abscissa was nondimensionalized in all and expressed as per cent duration systolic ejection. The individual values were then averaged at 21 points during the ejection period and the result appears in Fig. 2 B. Salient features of this representation are a rapid rise to peak power values during the first third of ejection, then maintenance of power output at a high level until half of the ejection period has been completed, and a subsequent slow decline in power

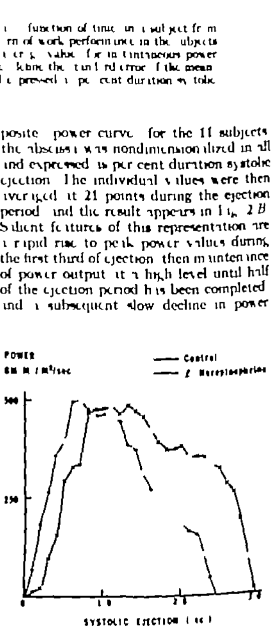


Fig. 3. Ventricular external power output in one individual (C.A. No. 18) at rest and during the administration of l-norepinephrine.

* ... are gratefully acknowledged from ... Center ... Cardiovascular ... Washington, D.C.

Table II Resting measurements in the subjects of Group I*

Patient (Number)	HR	P	CI	PW	KW	LVSW	LVMW	$\overline{LVSW}$
H L B (10)	58	133/80	3 35	88	1 5	90	5 270	83
A I (13)	65	127/84	2 94	73	1 3	74	4 810	71
J A (26)	66	136/79	3 53	88	1 1	89	5 874	85
W H P (7)	68	107/67	3 85	74	0 9	75	5 100	74
J Mc (30)	69	111/63	3 20	64	1 6	66	4 554	62
J W B (12)	71	112/69	3 08	60	0 7	61	4 331	58
W A H (11)	75	116/69	3 78	71	0 9	72	5 400	68
B W (19)	76	110/74	3 47	60	0 8	61	4 636	60
C A (18)	79	125/79	3 84	70	1 9	72	5 688	75
R L E (9)	106	124/85	3 36	50	1 1	51	5 406	50
I C (29)	112	117/70	3 80	50	1 0	51	5 712	48
Average	76 8	119/74	3 47	68 0	1 2	69 7	5 151	66 7
					±2 S D	25 6	1 037	

[illegible]

Table III Measurements during infusion of l norepinephrine

Patient (Number)	HR	P	CI	PW	KW	LVSW	LVMW
J M (30)	60	143/80	2 96	80	1 5	82	4 920
B W (19)	66	15 /94	3 11	86	0 7	87	5 743
C A (18)	69	163/100	3 33	95	1 3	96	6 6 4
I C (29)	75	154/90	3 71	95	1 7	97	7 275
Average	67 5	155/91	3 28	89 0	1 3	90 3	6 140
Per cent change	−20	+36/76	−8	+45	0	+45	+19

[illegible]

values over the last half of systole Although variations in the actual magnitudes of power output were found among individuals this temporal pattern of work performance was consistent and apparently unaltered by differences in heart rate

Values for rate pressure flow and work obtained during the administration of l norepinephrine are presented in Table III Increases in the stroke work index ranged from 24 to 90 per cent Because of the attendant bradycardia there was a lesser increase in minute work The kinetic fraction of the total work remained less than 2 per cent in these subjects

Accompanying the rise in stroke work with the pressor agent was a significant alteration in the temporal pattern of work performance Changes found in one subject are shown in Fig 3 whereas in Fig 4 the values for instantaneous power obtained in 4 individuals during infusion of the drug have been averaged and compared with their corresponding control observations With infusion of the drug the initial rise to peak power levels appears to be slightly delayed and values for peak

Table IV Measurements in individuals with heart disease

Patient (Number)	HR	P	CI	PW	KW	LVSW	LVMW
Group IIA							
M P (24)	73	124/70	3.35	66	0.5	67	4.891
H S P (22)	78	179/84	2.76	59	1.7	61	4.758
J W C (17)	79	153/83	3.46	74	0.8	75	5.925
H M (21)	80	135/82	3.33	68	0.9	69	5.520
R M C (20)	81	137/99	2.83	63	1.0	64	5.184
Average	78.2	136/84	3.15	66.0	1.0	67.0	5.256
Group IIB†							
E S (25)	71	107/69	2.43	45	0.4	45	3.195
J A C (16)	86	102/77	1.96	32	1.5	34	2.924
J M (23)	92	104/70	2.71	34	0.6	35	3.220
Average	83.0	104/72	2.37	37.0	0.8	37.8	3.113

*In patients with heart [illegible] control group

†These patients with [illegible] work [illegible] lower [illegible] control group

power output to be moderately increased The most prominent alteration is the maintenance of external power at a high level during the second half of systole Expressed in a different manner this means that with infusion of the drug approximately 11 per cent more of the total external work was accomplished during the latter half of systolic ejection (Fig 5)

Results obtained in the 8 individuals with heart disease (Group II) are presented in Table IV These patients were further subdivided on the basis of values for total work In 5 (Group IIA) mean pressures were generally higher and flows lower than those found in the control group Work indices were consequently within the range encountered in Group I The other 3 patients (Group IIB) had decreased values for both pressure and flow and the work accomplished was less than 50 Gm M /M per beat in all One of the subjects in this last group was in congestive failure at the time of study review of the clinical data in the other 2 patients revealed no obvious distinguishing characteristics at the time of study

Composite power curves were also different in the two subgroups (Fig 6) The pattern of work performance in those individuals in Group IIA resembles that seen with the administration of l norepinephrine with power output being maintained higher than in the normal subjects during the latter half of ejection On the other hand the Group IIB patients demonstrate a diminution in the absolute values for power output throughout This decrease is relatively greater in the first half of the ejection period however as can be seen from the comparisons of fractional work accomplishment in Fig 7

Discussion

Katz[7] in studies on the isolated turtle heart demonstrated that significant inaccuracy could arise from the use of mean pressure volume data to estimate stroke work Remington and Hamilton[8] found that the product of mean systolic pressure and stroke volume generally underestimated true ventricular work with the discrepancy usually being less than 12 per cent This is in agreement with the present study The difference is related to the contour of the pressure and flow wave forms and to neglect of the kinetic term In the limited range of stroke volumes and heart rates encountered in the present study the latter factor was not significant Under different circumstances particularly in the calculation of the work of the right ventricle this may not hold true[12]

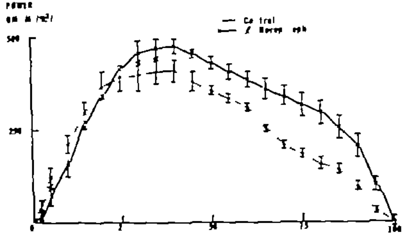


Fig. 4. External power output in 4 subjects at rest and during infusion of l-norepinephrine. The abscissa has been nondimensionalized and the vertical bars indicate the standard error of the mean. Values obtained during infusion of the drug differ significantly ($p < 0.05$) from the control over the last 55 per cent of ejection.

Factors governing the mechanical performance of cardiac muscle have recently been reviewed. These include the muscle's resting length, force-velocity relationships and afterload. In the isolated cat papillary muscle, l-norepinephrine increases work and power for any given initial length and afterload mainly by increasing the maximal velocity of shortening.[14]

Presumably analogous relationships will determine the mechanical performance of the intact ventricle.[9,15] At any given heart rate, the instantaneous power developed by the ventricle should be a function of end-diastolic volume, the inotropic state of the myocardium, and the output load imposed by the arterial system. Burch and his associates[16,17] have considered the variations in power output to be expected from alterations in heart rate occurring at constant level of pressure and cardiac output. In the intact subject such relationships become less easy to define. In the present study, an increase in the mean aortic pressure–mean flow ratio was common to those individuals receiving l-norepinephrine and to the patients with heart disease when compared with the control group. It is possible that this increase in resistive output load, rather than myocardial disease as such, is responsible for the relative increase in the levels of power during late systole. The lack of information concerning changes in ventricular filling pressure and contractile force, however, prohibits a satisfactory explanation of these alterations at this time. What is evident from the present study is that ventricular mechanical performance must be judged not only by the total work done but also by the temporal pattern of work accomplishment.

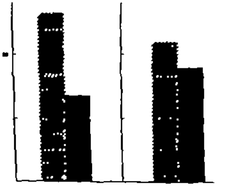


Fig. 5. Fractional work accomplishment during the first (*shaded bars*) and second (*solid bars*) halves of systolic ejection before and during infusion of l-norepinephrine. The relative increase in work performed during the second half of the ejection period is statistically significant ($p < 0.05$).

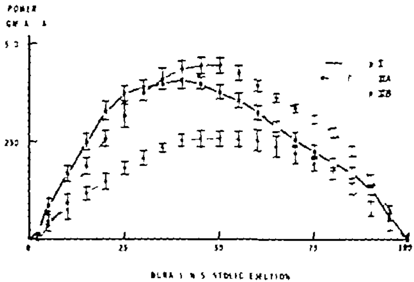


Fig 6 External power output in subjects without cardiovascular disease (Group I and in those with primary myocardial disease (Group II) Values for stroke work were above 60 Gm M /M per beat in the 5 patients in Group IIA and below 50 Gm M /M per beat in the 3 subjects in Group IIB Vertical lines represent the standard error of the mean

Finally it should be mentioned that a portion of the output load faced by the ventricle is nonresistive in nature and reflects the inertial and compliant properties of the system upon which work is being done This means that not only the dissipation of power but also the storage of energy may take place In the steady state the power stored would not influence the total external work done by the ventricle but could alter the temporal manner of its accomplishment The effect of the complex output load on ventricular power output is difficult to analyze in terms of the temporal pressure flow product an approach based on the study of the transmission of power in the ascending aorta has been presented in a preliminary report [1]

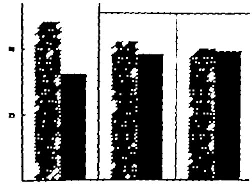


Fig 7 Fractional work accomplishment during the first (*shaded bars*) and second (*solid bars*) halves of ejection in Groups I and II The difference between the control group and the two groups with heart disease is statistically significant (p < 0 02)

Summary

1 Measurements of the external work and power of the left ventricle have been made in 19 subjects Computations were based on instantaneous measurements of pressure velocity and flow in the ascending aorta

2 In 11 subjects without known cardiovascular disease the resting stroke work index ranged from 51 to 90 Gm M M per beat The average minute work index was 5 2 Kg M M per minute in the same group

3 The administration of l norepinephrine produced not only a rise in the total work performed but also a change in the temporal pattern of work accomplishment whereby the increase in power output was most pronounced during the latter half of the ejection period

4 In 6 individuals with nonvalvular heart disease but normal external work

output increases in external power during late systole relative to the normal were found In 3 subjects with work values below 50 Gm M /M per beat there was both a general diminution in the levels of power achieved and an altered pattern of work performance

5 The factors relating to the manner of work accomplishment by the intact ventricle have been discussed

The helpful suggestions received from Dr Gerald Shugoll in regard to this study are gratefully acknowledged

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Case reports

Anomalous origin of the left coronary artery from the pulmonary artery

A therapeutic problem

*L. G. Van der Hauwaert, M.D.**
G. L. Stalpaert, M.D.
L. Verhaeghe, M.D.
Louvain, Belgium

Anomalous origin of the left coronary artery from the pulmonary artery is one of the rarest causes of cardiomegaly and heart failure in infancy. According to Agustsson and associates, some 75 cases had been reported up to 1962.

Interest in this condition has been growing in recent years because of a reappraisal of the resulting hemodynamic upset. The old concept of Brooks that the anomalous coronary artery might function as a vein, thereby constituting a coronary arteriovenous fistula, has recently been widely accepted. Furthermore, a new surgical approach based on this physiologic concept has been advocated and consists in ligating the anomalous vessel.

We are presenting the clinical and pathologic findings in a 4 month old baby who underwent such an operation and who died within the first postoperative hours. Postmortem coronary angiography was performed and will be discussed in some detail.

Case report

This baby girl was first admitted at the age of 4 months, having been born normally after an uncomplicated pregnancy. The parents had never noticed anything remarkable until 3 weeks before admission, when the baby began to cough and wheeze. The family doctor treated the patient for bronchitis, apparently without much benefit. Two days before admission the baby became very dyspneic and developed noisy respiration. Colicky pains while feeding had never been noticed.

On admission the infant was restless and in acute distress with a labored respiration at 84 per minute. There was slight generalized cyanosis. Weight and length were normal for age. Widespread moist râles made careful cardiac auscultation difficult. The liver was felt 5 cm. below the right costal margin. The clinical impression was that the baby had bronchopneumonia complicated by congestive heart failure.



Fig. 1. Chest radiogram showing massive cardiac enlargement and congestion of the hilar region.

From the Department of [illegible] Medicine and Surgery, University Clinic, [illegible] Louvain, Belgium.
Received for publication May 8, 1964.
*Address: Department of Medicine, [illegible] University Clinic St. Raphael, Louvain, Belgium.

Oxygen and intramuscular digoxin were administered at once and an intravenous infusion of hydrocortisone Chloromycetin and Achromycin was started Within 24 hours a striking improvement was attained Cardiac auscultation now revealed a soft Grade 2/6 blowing pansystolic murmur at the apex The latter was displaced to the mid axillary line The chest x ray film (Fig 1) showed a large uniformly dilated heart almost touching the left thoracic wall The lungs were congested but seemed to be free of bronchopneumonic infiltrations

The electrocardiogram (Fig 2) showed a regular sinus rhythm and a mean electrical QRS axis of −10 degrees Deep Q waves and sharply negative T waves were seen in Leads I aVL V Vs and V6. The R potentials in the left precordial lead which were as high as 45 mm in Lead V6 and 30 mm in Lead V indicated marked left ventricular hypertrophy

In view of these typical electrocardiographic findings (anterolateral infarction and left ventricular hypertrophy) the diagnosis of aberrant left coronary artery seemed to be highly probable Therefore cardiac catheterization and angiocardiography were considered to be unnecessary in this critically ill patient

Since the prognosis of this condition is very poor it was decided to try the surgical treatment first suggested by Case and associates[8] namely ligation of the aberrant coronary artery After 1 month of medical therapy the baby seemed to be in optimal condition to undergo this operation Râles were no longer heard the heart rate had come down to 120 130 per minute and the liver was only 2 cm below the costal margin There was however no decrease in the size of the heart and the electrocardiogram remained unchanged

A bilateral thoracotomy below the fourth rib and section of the sternum were performed The massively enlarged heart was very irritable After the pericardium was opened the left ventricle appeared to be much paler and to contract less vigorously than did the right ventricle A communication between the left coronary artery and the pulmonary artery was found just proximal to its bifurcation into the anterior descending and left circumflex arteries A ligature was passed around the vessel at its origin from the pulmonary artery and transient occlusion was tried No disturbances in rhythm or increasing ischemic changes were noted on the electrocardiogram which was monitored continuously throughout the procedure Subsequently the anomalous vessel was ligated Some talcum powder was introduced into the pericardial sac before closing it The immediate postoperative hours were uneventful but 18 hours after operation the child went into acute cardiac failure from which it could not be resuscitated

Autopsy was restricted to the heart and great vessels The heart weighed 70 grams or approximately three times the normal weight at age 4 months The anomalous origin of the left coronary artery from the pulmonary artery was confirmed The left ventricle appeared to be fibrotic in its lateral aspect

Before the heart was incised coronary angiography was carried out A cannula was inserted into the ostium of the right coronary artery and a small amount of barium sulfate was injected under manual pressure Radiographic pictures in the frontal and lateral projections were made at regular intervals (Fig 3) Almost from the beginning of the injection into the right coronary artery radiopaque material seemed to cross the interventricular septum and to fill the anterior descending branch of the left

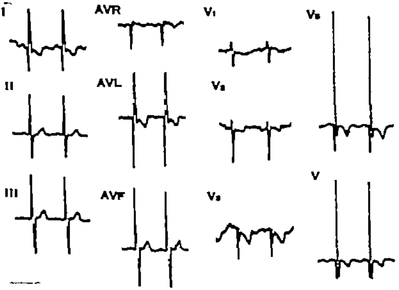


Fig Electrocardiogram demonstrating deep Q waves in Lead I aVL V V and V6. High R potentials and sharply inverted T waves are seen in the left precordial leads

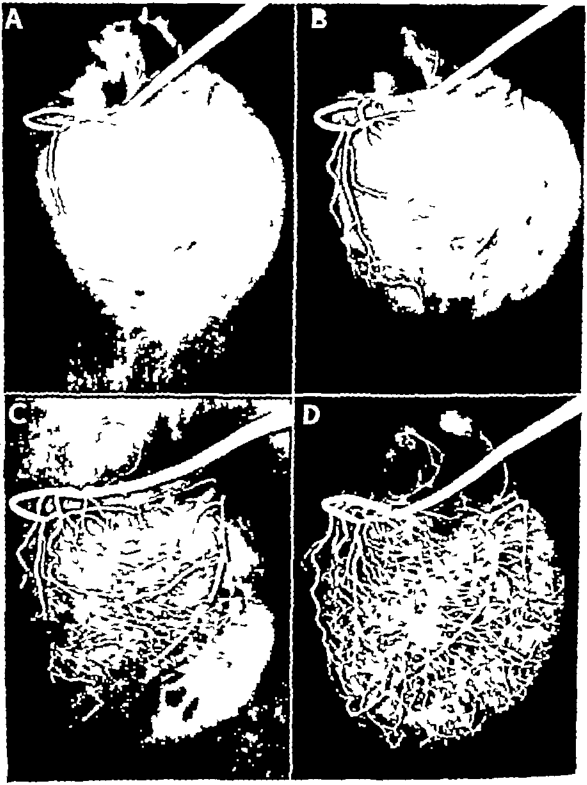


Fig. 3. Postmortem coronary angiograms. The cannula was inserted into the ostium of the normal right coronary artery, and a barium sulfate suspension was injected under minimal pressure. Successive phases of the injection are represented in A, B, C, and D. Almost from the beginning (B) radiopaque dye spilled over into the anterior descending branch of the left coronary artery. Later (C and D) the whole left coronary artery system was filled through multiple but small anastomotic channels between both coronary arteries.

coronary artery in its distal part (Fig. 3 B). This occurred even before the smaller arteries of the right coronary system were filled. Eventually, the barium suspension filled all branches of the anomalous coronary artery up to the site at which the surgical ligature prevented its entry into the pulmonary artery (Fig. 3,D).

The anomalous left coronary artery originated from the sinus of the left posterior pulmonary cusp. Its main trunk ran inferiorly along the interventricular sulcus and followed the distribution of the anterior descending branch of the left coronary artery. A smaller branch followed the course of the left circumflex artery. The right coronary artery was normal in its origin and distal distribution.

Multiple small anastomotic channels between the right and left coronary systems were found in the interventricular septum. A few could be followed over the anterior and posterior surfaces of the heart. None of them was wide enough to secure a continuous and free communication between the main branches of both sides.

By means of the technique described by Vastesaeger and associates, the diameter of intercoronary anastomoses can be fairly accurately measured on radiographic photographs. The diameter of the largest anastomoses was thus estimated to be between 150 and 200 μ. The thickness of the right ventricle was 2 mm. in the inflow region and 3 mm. in the outflow tract. The left ventricle was grossly dilated and its wall measured 5 mm.

A large organized thrombus (3 cm. in diameter) was found in the cavity of the left ventricle and was firmly adherent to the wall. The endocardium of the left ventricle was thickened and fibrotic. All valves were normal.

Histologically, large zones of patchy fibrosis were found in the myocardium of the left ventricle. No fresh myocardial necrosis was observed.

The left coronary artery was not dilated nor tortuous. On microscopic slides its wall was slightly thinner than that of the right coronary artery sectioned at a comparable distance from the ostium. The muscular media was well developed and nothing suggested a veinlike structure of this vessel.

Discussion

The clinical and electrocardiographic signs presented by infants with anomalous origin of the left coronary artery have been the subject of several reports and have recently been summarized by Keith.[3] As in our case, the diagnosis should be suspected whenever an infant in the first year of life develops cardiomegaly and congestive heart failure in the absence of significant murmurs and shows electrocardiographic evidence of anterolateral myocardial infarction.

The clinical picture of the so-called adult type is on the whole quite different.[1] Symptoms are minimal or absent but sudden death has been reported. A heart murmur, either systolic or continuous, is often the main reason for further cardiac investigation. The electrocardiogram may be normal or may show left ventricular hypertrophy, occasionally with changes in the S-T segment or T wave suggestive of myocardial ischemia. As far as we were able to find out from the literature, *not a single patient over the age of 2 years showed electrocardiographic evidence of a transmural anterolateral infarction.*

Recently a few interesting case reports have been published on patients who presented signs of severe congestive heart failure in infancy without the typical electrocardiographic changes of myocardial infarction.[4,7] They became asymptomatic later on in childhood and gradually developed the clinical signs of the adult type.

Catheterization reports mainly concern older children and adults. In these, a small to moderate increase in oxygen saturation is usually demonstrated at the level of the pulmonary artery.[1,4] In infants, however, no such left-to-right shunt is observed.[8]

Aortography with the tip of the catheter placed above the aortic valve seems to be the most valuable diagnostic technique in both age groups. It also offers direct proof, at least in adults, that the anomalous left coronary artery functions as a vein, as was first suggested by Brooks and more recently by Edwards.[11] Lampe and Verheugt[8] were the first to demonstrate by *aortography in a 16-year-old boy that* the direction of the flow was from a tortuous and dilated right coronary artery through large anastomotic channels into the left coronary artery and hence into the pulmonary artery.

It should be noted that dilated tortuous coronary arteries or massive filling of the pulmonary artery, or both, suggestive of a considerable left-to-right shunt through the arteriovenous coronary fistula, have been demonstrated in all adults and older children in whom aortography was performed.[1,4]

In infants, however, either no visualization of the left coronary artery or poor opacification of this vessel without tortuosity and without subsequent filling of the pulmonary artery is seen.[11] Moreover

angiographic studies suggest that in infants the flow of blood may occasionally be from the pulmonary artery to the aberrant left coronary artery [8,13]

On the basis of the clinical hemodynamic and angiocardiographic evidence the following conclusions seem to be warranted In older children and adults who have survived because they have developed sufficient intercoronary anastomoses the main physiologic handicap results from a coronary arteriovenous fistula and the ensuing left to right shunt Although the perfusion pressure in the left coronary artery is low the flow of blood into its peripheral branches is presumably adequate and myocardial infarction does not occur On the other hand in newborn and small infants the basic factors which determine the clinical condition and eventual survival are the actual development of intercoronary anastomoses and the pulmonary arterial pressure Indeed as long as the pulmonary arterial pressure is high in the neonatal period blood flow into the aberrant left coronary artery may be predominantly from the pulmonary artery and few functioning intercoronary anastomoses are required for survival If the latter are sufficiently large by the time pulmonary arterial pressure decreases in the first weeks of life little myocardial ischemia follows or gives rise only to a nonspecific cardiomegaly without electrocardiographic evidence of transmural infarction As the intercoronary anastomoses develop the left ventricle derives its supply of blood more and more from the right coronary artery and the aorta These patients are able to survive into adulthood In the absence of large anastomotic channels however the physiologic decrease in pulmonary vascular resistance and pulmonary arterial pressure in the neonatal phase will soon result in a deficient flow of blood into the left coronary artery and myocardial infarction

There is little hemodynamic and angiographic evidence for the alternative explanation that myocardial infarction in infants would be due primarily to large intercoronary anastomoses allowing massive escape of the coronary blood flow into the low pressure zone of the pulmonary artery and producing inadequate perfusion pressure in the peripheral branches of the left coronary artery Moreover older children and adults who do have a large left to right shunt through the arteriovenous coronary fistula rarely exhibit myocardial ischemia

Postmortem coronary angiography in our case clearly demonstrated the existence of multiple anastomotic vessels between both coronary arteries However the functional importance of these anastomoses should not be overestimated since their cross section was small varying from 150 to 200 μ Anastomoses of comparable size have been found in normal newborn infants [1] According to Vastesaeger and associates [1] the cross section of intercoronary arteriolar communications in the normal fetal or neonatal heart vary from 70 to 200 μ

The anatomic and physiologic differences between the infantile and adult types seem to be reflected in the surgical results Ligature of the aberrant left coronary artery has been reported by nine authors in 16 patients [3,5,7,9,10,1,15,17] All 8 patients over the age of 2 years who were operated upon survived and their cardiac condition was restored to normal [3,7,9,10,11] Five of the 8 infants who were under 2 years of age died The 3 surviving babies apparently benefited from the operation but cardiomegaly and electrocardiographic evidence of ischemia or infarction persisted [1,15,17]

Ligation of the aberrant coronary vessel may be harmful to some infants in whom the flow of blood is from the pulmonary artery to the left coronary artery It also appears to be contraindicated in those patients in whom the flow of blood in the left coronary artery is limited by the small size of the intercoronary communications In these instances the ideal surgical treatment would be to accomplish an anastomosis between the aberrant coronary vessel and a systemic artery So far these attempts have been unsuccessful [15,18] A less radical approach would be to promote intercoronary anastomoses by the introduction of talcum powder into the pericardial sac [18,19]

Our experience confirms the views of Stern and associates[14] and Jameson and co workers[9] that only infants who exhibit a considerable left to right shunt through the coronary arteriovenous fistula and

whose condition resembles the adult type could be expected to benefit from the ligation of the anomalous coronary artery. It is of paramount importance, therefore, to perform a complete cardiac catheterization and aortography in all babies who are suspected of having this anomaly, even if the diagnosis is very probable on account of the electrocardiogram. Only in this way will a better surgical selection be possible.

Summary

A case of an anomalous left coronary artery originating from the pulmonary artery is described. The infant, 4 months old, died shortly after ligation of the aberrant vessel. Postmortem angiography demonstrated multiple small anastomotic channels with a cross section varying from 150 to 200 μ between the right and left coronary arteries.

The physiologic disturbances resulting from this anomaly are discussed briefly, and the differences between the infantile and adult types are stressed.

It is suggested that the anomalous left coronary artery should only be ligated if a left-to-right shunt through it can be demonstrated by cardiac catheterization or aortography.

We are most grateful to Dr. Hamish Watson for his comments and helpful criticism.

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Constrictive pericarditis after blunt chest trauma

*Sidney Goldstein, M.D.**
Paul N. Yu, M.D.
Rochester, N. Y.

The purpose of this paper is to report and emphasize the development of constrictive pericarditis after nonpenetrating chest trauma. Blunt chest trauma has been demonstrated to cause severe pericardial and myocardial damage in man and animal.[1-3] In a number of cases, hemorrhagic pericardial effusions with the subsequent formation of pericardial adhesions have been described following nonpenetrating trauma. Tabatznik and Isaacs[4] described the postpericardiotomy syndrome that follows both penetrating and nonpenetrating wounds of the chest. To our knowledge, however, only eight reports of constrictive pericarditis occurring after blunt trauma have appeared in the English literature.

The present report describes 4 cases of constrictive pericarditis resulting from blunt trauma to the chest and adds further information in regard to the relationships of postpericardiotomy syndrome to the subsequent development of constrictive pericarditis.

Case reports

Case 1. J. C. T., a 20-year-old white farmer, was admitted to the Strong Memorial Hospital on Jan. 5, 1948. In March 1947 he had received a crush injury while playing basketball, followed by persistent dull aching in the anterior thorax. By September 1947 his abdomen began to swell, and in October his liver was found to be enlarged. In December of the same year he noted ankle edema which gradually progressed up his legs, disappearing at night and reappearing when he began to move around. On several occasions during the week prior to admission he also noticed slight swelling of his cheeks and soft tissue of the neck on arising in the morning.

Physical examination on admission showed a blood pressure of 100/72 mm. Hg. The heart was normal in size, without murmurs. A diastolic gallop was present. The liver was enlarged to four fingerbreadths below the costal margin, and evidence of free fluid in the peritoneal cavity was present. Fluoroscopy of the chest showed slight enlargement of both the left and right ventricles. The pulsations of the heart were of poor quality. Liver biopsy showed passive congestion of the liver. Venous pressure was 33 cm. of water. Total protein was 4.7 Gm. per cent, with 2.3 Gm. per cent of albumin. A 12 lead electrocardiogram demonstrated sinus tachycardia, inverted T waves in Leads I, II, III, and V, and low voltage of the QRS complex. Circulation time from arm to lung with ether was 40 seconds, and that from arm to mouth with Decholin was 46 seconds.

Cardiac catheterization was attempted on March 26, 1948, at which time only a right atrial pressure was recorded. This demonstrated a W pattern strongly suggestive of constrictive pericarditis. He lost his edema on bed rest and low-salt diet while in the hospital.

Exploration of the chest was decided against because of his improvement and the possibility of a reversal of the process. He was discharged on

From the Cardiopulmonary Laboratory, Rochester General Hospital and the Strong Memorial Hospital, and the Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.
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*Rochester General Hospital, Research Division, 500 West Main St., Rochester, N. Y. 14608.
†Previously reported.

Feb 28 1948 but was readmitted on June 10 1948 because of recurrent swelling of his ankles and full ness of the abdomen A pericardiectomy was per formed At operation the apex of the heart and the pleura were found to be very much adherent to the pericardium The pericardium was pale thickened and fibrous The pulsations of the heart were very quiet A the thickened pericardium was removed the heart muscle herniated through the opening and the cardiac action became much more forceful At the close of the procedure the heart was found to have good pulsations Pathologic section of the tissue taken during operation confirmed the diag nosis of chronic pericarditis

The patient did quite well after the operation He was seen again in 1967 at which time he had had no recurrence of symptoms

Case 2 K. C. a 28-year-old laborer was seen at the Strong Memorial Hospital in July 1953 In 1950 3 years prior to admission he was struck over the left anterior chest with a heavy piece of farm equipment. He stated that the injury necessitated strapping of his chest for about 2 weeks A chest roentgenogram was taken at that time In August of 1952 he was rejected by the Army because of heart disease and in January 1953 he had a probable viral infection at which time he noted some moderate increase in exertional dyspnea palpitation and constant dull radiating pain in the left anterior chest He had one episode of paroxysmal nocturnal dyspnea His symptoms became stable for about 2 months and then returned in April 1953 at which time an electrocardiogram taken by his physician showed inversion of the T wave in the left precordial lead

On admission he was a well nourished well developed white man lying flat in bed with no cyanosis peripheral edema or clubbing The neck veins were slightly distended The heart was not enlarged The first sound was loud No murmurs were heard The second sound in the pulmonary area was accentuated and duplicated The lungs were clear The liver was felt two fingerbreadth below the costal margin

A 12 lead electrocardiogram showed a +90 degree axis with equal amplitude of R and S waves in Lead V and broad and notched P waves in Leads II III and aV L. The heart was not enlarged on the chest roentgenogram and fluoroscopically the pulsations of the heart were diminished

At cardiac catheterization the right ventricular pressure pulse demonstrated a high end-diastolic plateau and was typical of constrictive pericarditis It was 24/11 mm Hg at rest and 3 /19mm Hg with exercise The cardiac index was 2 60 L./min /M this increased to 3 4 L/min /M with exercise The right atrial pressure was 1 mm Hg and the brachial arterial pressure was 108/ 0 mm Hg

On July 7 1953 thoracotomy revealed a thickened and calcified constricting pericardium The pericardium was dissected from the right and left ventricular and atrial surfaces of the heart Microscopic description of the removed pericardium was that of fibrous tissue with chronic inflammatory cells

The patient was seen again on Nov. 24 1953 at which time a repeat cardiac catheterization was performed The cardiac index was 3 68 L /min /M the right ventricular pressure was 21/4 the right atrial pressure was 3 and the pulmonary wedge pressure was 7 mm Hg The patient has done well and is asymptomatic at the time of this writing

Case 3 M R was seen at the age of 14 years at the Rochester General Hospital in 1942 Her history was that 5 months prior to admission she had been struck in the left anterior chest and shoulder with a dodge ball This was a sudden blow accompanied by some pain and associated with a sudden and short syncopal episode The following day she had fever and chill which persisted for 4 days This was associated with an increase in the pain on the left side of her chest After 2 weeks the pain and fever gradually subsided She lost approximately 15 pounds of weight in the ensuing 6 weeks but returned to school and felt perfectly well One month prior to admission she noticed swelling of her abdomen and a slight gain in weight

On admission she had an enlarged heart with poor pulsations and free fluid in the peritoneal cavity Venous pressure was 22 cm of water measured at the level of the right atrium Circulation time was 22 seconds from arm to tongue An initial paracentesis removed 5 000 ml of fluid and the venous pressure fell to 16 cm of water At that time the liver was felt three fingerbreadths below the right costal margin Because of the suggestion of constrictive pericarditis pericardiectomy was performed under local anesthesia Operation revealed a thick and densely fibrotic pericardium which was closely adherent to the entire left and right ventricles Dissection was carried as far laterally as the local anesthesia permitted Postoperatively she did only moderately well Fluoroscopy of the chest still demonstrated poor pulsations of the heart She was treated with digitalis preparation and mercurial diuretics In the succeeding 5 years she did fairly poorly She had recurrent ascites which required frequent paracenteses She also had increased dyspnea and fatigue From 1951 to 1956 she improved considerably and required no further paracenteses Her fatigue and dyspnea markedly diminished

In 1956 she was readmitted to the Strong Memorial Hospital for diagnosis At that time she had mild dyspnea on exertion and was able to climb one flight of stairs She had no ankle edema The blood pressure on admission was 100/72 mm Hg The neck veins were distended at 30 degrees There was dullness in the left lower back The left border of cardiac dullness could not be determined The heart sounds were of good quality There were no thrill The abdomen was protuberant and the liver was palpable 4 cm below the right costal margin The tip of the spleen was barely palpable Fluoroscopy showed that there was a considerable amount of calcium around the pericardial sac and pulsations of the heart were diminished No enlargement of any specific chamber was demonstrable A 12 lead electrocardiogram showed a P R interval of 0 21 second and low voltage of the QRS complex.

Cardiac catheterization was unsuccessful because of venous spasm Because of the elevation of venous pressure the patient was thought to have continued

constrictive pericarditis. A thoracotomy performed through a median sternotomy incision showed a very much thickened and calcified pericardium. In addition there was an empyema cavity in the left chest. The calcified pericardium was removed

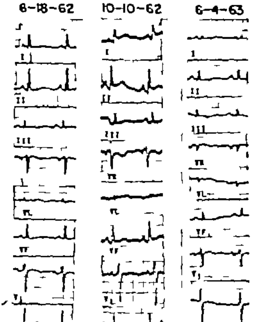


Fig. 1. Case 4. Serial electrocardiograms after chest trauma. *Left.* Tracing taken after acute trauma. *Center.* Tracing recorded during the time of acute pericarditis. *Right.* Tracing taken at the time of constrictive pericarditis demonstrating decreased voltage of QRS complex.

and the purulent fluid in the empyema cavity was drained through the left anterior chest. Postoperatively the patient did well and had no complications. The venous pressure returned to normal some 7 months later although the size of the heart was unchanged. When she was seen again in 1961 she had no dyspnea, fatigue, or abdominal distention. Fluoroscopy of the chest showed normal pulsations of the heart.

Case 4. J. G., a 74-year-old retired cabinet maker, was in good health until June 6, 1962, when he was involved in a head-on automobile collision. In the accident he was thrown against the steering wheel and suffered chest contusions and multiple fractures of the sternum and anterior ribs bilaterally. He was hospitalized at the Rochester General Hospital for 3 weeks, during which time he was critically ill. His temperature ranged up to 102-103° F. for 9 days and a tracheotomy was performed to maintain an adequate airway. Numerous blood transfusions were required because of profuse hemoptysis. He was dyspneic with bilateral pulmonary râles and distended neck veins. Digitalis therapy was instituted. He gradually improved and was discharged. The electrocardiogram is shown in Fig. 1. A chest roentgenogram (Fig. 2A) at that time showed that the heart was of normal size.

After discharge from the hospital he never felt quite well and complained of a mild degree of weakness. On Oct. 10, 1962, the patient developed tight anterior chest pain associated with a nonproductive cough. This lasted for approximately 2 weeks and was associated with a daily fever of 101° F. The patient was seen by his local physician, who took an electrocardiogram (Fig. 1) and a chest roentgenogram (Fig. 2B). The electrocardiogram showed S-T and T abnormalities indicative of acute pericarditis, and the chest roentgenogram demonstrated an increase in the cardiac silhouette suggestive of pericardial effusion. Treatment with aspirin led to a return of his temperature to normal and a subsidence of his chest pain. After this episode he felt relatively well but still complained of weakness and easy fatigue. In January, 1963, the patient developed rapid atrial fibrillation. He was again treated with digitalis, with a reversion to normal sinus rhythm after 1 week. Digitalis was again discontinued and the patient felt relatively well until March, 1963, when he gradually developed swelling of the ankles, a mild degree of orthopnea, exertional dyspnea, and increased fatigue. Because of these symptoms he was admitted to another hospital on April 15, 1963, where he again received digitalis preparations and diuretics with immediate relief of his ankle edema and improvement in the dyspnea. He was discharged from this hospital on digitalis and oral diuretics, but in spite of an adequate low salt diet the ankle edema and dyspnea recurred and he was referred to the Rochester General Hospital.

At the time of examination the patient complained of one flight dyspnea on exertion, three-pillow orthopnea, and marked ankle edema. In addition he had a moderate degree of abdominal bloating and fullness.

The patient was an elderly white man who was in moderate respiratory distress. His blood pressure was 130/70 mm. Hg with no pulsus paradoxus



Fig. 2A. Case 4. Roentgenogram recorded June 21, 1962 after acute trauma.



Fig. 2B. Case 4. Roentgenogram recorded Oct. 16, 1962 at the time of acute pericarditis demonstrating pericardial effusion.

The pulse rate was 80 per minute and respirations were 16 per minute. Funduscopy revealed some engorgement of the retinal veins. The jugular veins were distended when the patient was in an upright position with prominent a and v waves and rapid y descent. The lungs were clear to percussion and auscultation except for a pleural pericardial friction rub in the anterior chest. The left border of cardiac dullness was inside the mid-clavicular line. At the apex the first sound was greater than the second sound. In the pulmonary area the second sound was physiologically split. There was a very loud diastolic gallop. The liver was felt four fingerbreadths below the costal margin but the spleen and kidneys were not palpable. There was 3+ ankle edema in the lower extremities. Routine laboratory tests showed a hemoglobin of 13.4 Gm. per cent and the white blood count was 6,900. The electrocardiogram demonstrated low voltage of the QRS complex throughout the entire precordium (Fig. 1). A chest roentgenogram disclosed normal cardiac silhouette with pulmonary congestion (Fig. 2C). The venous pressure was 240 mm. of saline at the level of the right atrium.

Cardiac catheterization was performed on June 11, 1963. The cardiac index was 2.6 L./min./M.² and the right ventricular pressure was 34/22 mm. Hg (Fig. 3). Since a diagnosis of constrictive pericarditis was strongly suspected, an exploratory thoracotomy was performed on June 19. The cardiac pulsations were markedly decreased. When a small incision was made through the pericardium, the ventricular wall bulged through. The pericardium was closely adherent to the epicardium. The peri



Fig. 2C. Case 4. Roentgenogram recorded May 1963 at the time of constrictive pericarditis.

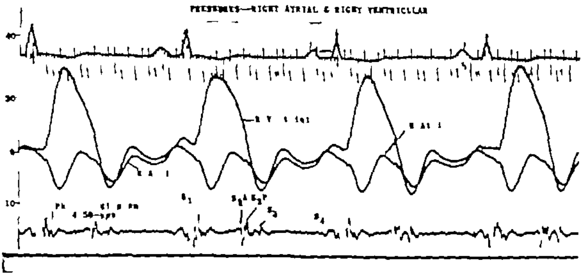


Fig 3 Case 4 Recordings of right ventricular and right atrial pressures which demonstrate the typical pattern f constrictive pericarditis A prominent diastolic gallop is recorded

ardium measured 2 to 3 mm at its greatest thickness and was easily stripped from the epicardial surfaces of the heart Pericardiectomy was carried out from the left phrenic nerve to the right atrial wall and pleuropericardial reflection The patient's postoperative course was uneventful His venous pressure fell to 140 mm and his liver was felt only one fingerbreadth below the costal margin at the time of discharge Pathologic report of the pericardial biopsy revealed dense fibrous tissue inflammatory cells and deposits of hemosiderin

Since discharge the patient has done quite well and is much improved symptomatically He has been maintained on digitalis therapy but has required no further diuretic medications At the time of this writing his liver is no longer palpable and the neck veins are flat with normal venous pressure

Discussion

Many authors have reviewed the incidence of trauma to the heart that follows severe direct chest and body trauma[1,16] Lenoff[8] stated that 16 per cent of 50 unselected fatal automobile accidents demonstrated gross trauma to the heart Sigler[16] placed the incidence at 79 per cent of cardiac injuries occurring after direct chest trauma Kissane[1] studied the effect of chest trauma in both man and animal and demonstrated hemorrhage edema and fragmentation of myocardial fibers in addition to pericardial hemorrhage After chest trauma depression of the S T segment and flattening of the T wave may occur and may persist from 15 to 30 days[17] Tabatznik and Isaacs[4] studied the development of the postpericardiotomy syndrome after both blunt and penetrating cardiac trauma In their series of 50 cases 11 developed recurrent pyrexia and chest pain associated with pericardial effusion These symptoms persisted and recurred for up to 1 year and occasionally required pericardiectomy in order to prevent the recurrence of these effusions At the time of operation for recurrent effusion areas of loculated effusion and adhesions have been described along with early development of pericardial thickening[4]

There have been a number of well documented cases of constrictive pericarditis which developed 1 to 2 years after blunt chest trauma The first such case was reported by White and Glendy[18] in their review of 31 cases of Pick's disease at the Massachusetts General Hospital In one of their cases a severe blow to the chest preceded symptoms of a bloody pericardial effusion which later developed into chronic tuberculous constrictive pericarditis They suggested that pericarditis after chest trauma may be related to a breakdown of tuberculous nodes in the pericardium However no subsequent case associated with tuberculous infection has been reported Glenn[7] reported the first case of constrictive pericarditis that followed blunt trauma in an automobile accident and it was very similar to our

Case 4. His patient developed symptoms of constrictive pericarditis 2 years after the trauma. The exact incidence of constrictive pericarditis after both blunt and penetrating chest trauma is difficult to assess. Follow-up series of chest trauma have failed to demonstrate any occurrence of constriction.[4, 5]

The progress of this disease was clearly outlined in Case 4. The patient had a very stormy post-trauma course which was probably complicated by an unrecognized hemopericardium and congestive heart failure. Four months after his initial trauma he developed definite evidence of acute pericarditis and pericardial effusion. This effusion persisted for a number of months but was asymptomatic. Nine months after his trauma, he developed definite signs of constrictive pericarditis. Cases 1, 2, and 3 also had persistent chest pain and occasionally fever for a number of weeks after trauma. They developed their symptoms of constrictive pericarditis from 6 months to 2 years after trauma.

It should be pointed out, however, that the evidence of constrictive pericarditis on the basis of previous chest trauma in these 4 cases must be considered to be only circumstantial. In these cases the history at the time of their initial examination strongly suggested that the trauma described was related to the development of the disease. It is admittedly difficult to establish the relationship and to clearly rule out the presence of any existing disease prior to chest trauma.

The etiology of constrictive pericarditis that develops after blunt trauma has been open to speculation for some time. Baker[11] suggested that the large blood clots in the pericardium may behave like similar ones in the subdural space which liquify and split protein molecules into smaller moieties. The resultant rise in osmotic pressure attracts more fluid into the pericardial space. He suggested that in addition, the organization of hemorrhagic fluid in the pericardial cavity leads to adhesions and thickening. Ehrenhaft was unsuccessful in producing constrictive pericarditis by injecting autologous blood into the dog pericardium. However, he was able to produce some pericardial thickening by injecting lipid fraction of pooled dog blood.

The similarities of this syndrome to the postpericardiotomy syndrome[1] after cardiac surgery have been pointed out by other authors. In the postmyocardial infarction syndrome, in which hemorrhagic pericardial effusions may occur in the absence of anticoagulant therapy, patients may develop recurrent effusions associated with fever and organized pericarditis.[?]

Since patients with effusions due to blunt trauma as well as the postmyocardial infarction and commissurotomy respond to adrenocortical steroid therapy,[1?, ?] it has been suggested that these may all represent autoimmune disease. However, laboratory evidence of such an antigen-antibody reaction has not been demonstrated as yet.

In view of the increased frequency of automobile accidents and blunt chest trauma due to other causes, the occurrence of the postpericardiotomy syndrome and pericardial constriction secondary to trauma should be considered in the etiology of acute pericarditis and constrictive pericarditis. In older patients, the development of congestive heart failure and edema may be ascribed to forms of heart disease other than pericardial disease. A history of chest trauma in patients with fluid retention and marked venous hypertension in excess of cardiac disability should make one suspect the development of constrictive pericarditis.

Summary

Four cases of constrictive pericarditis that followed blunt trauma are reported. Documentation of a postpericardiotomy syndrome occurring 5 months after trauma in one patient was noted, and the time relationships of trauma, postpericardiotomy syndrome, and constrictive pericarditis are outlined.

Dr. Earle B. Mahoney performed the pericardiectomy in Cases 1 and 2. Dr. William Farlow and Dr. Mahoney performed the cardiac surgery in Case 3. Case 4 was referred to us by Dr. Salvatore Pomer and the operation was performed by Dr. Robert Weiner.

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Clinical pathologic conference

Robert C. Speckhals, M.D.
Paul Winchell, M.D.
Kurt Amplatz, M.D.
*Jesse E. Edwards, M.D.**
Arthur H. L. From, M.D.
St. Paul and Minneapolis, Minn.

Clinical abstract

DR. SPECKHALS: A 22-year-old white woman in the eighth month of her first pregnancy was admitted to the hospital for the first time with the chief complaints of cough, dyspnea, and orthopnea.

The patient had noticed the onset of a nonproductive cough approximately 6 weeks prior to admission. This was not associated with fever, chills, or hemoptysis. For 10 days prior to admission, increasing dyspnea on exertion had been noticed. Early on the morning of admission an episode of sudden onset of orthopnea and an increase in the degree of dyspnea and cough was experienced. The patient denied having thoracic pain, chills, fever, abdominal pain, or swelling of the ankles. There was no history of any recent febrile illness, hypertension, or albuminuria. There had been no significant gain in body weight.

The past history revealed that an episode of acute glomerulonephritis had occurred when she was 5 years old. No significant neuromuscular symptoms were reported and there was no history of swelling or pain in joints. Two [illegible] had had rheumatic fever.

Physical examination revealed a well-developed, well-nourished, white, pregnant, acyanotic woman, dyspneic and orthopneic, who appeared to be acutely ill. Except for signs of pregnancy consistent with the history, the positive physical findings were related to the cardiovascular system. The pulse was regular and the rate was 100 per minute. There was no fever. The blood pressure was 94 mm. Hg systolic and 60 mm. Hg diastolic. No cervical [illegible] distention was apparent, and there was no edema of the extremities. Palpation of the precordium revealed a left ventricular thrust. The pulmonic component of the second sound was accentuated. A third heart sound, not typical of an opening snap, was heard early in diastole. A Grade 2/6 systolic ejection type of murmur was present over the cardiac apex. No diastolic murmur was noted. A few râles were present at the pulmonary bases. The thyroid gland was diffusely enlarged to a minor degree.

An electrocardiogram revealed a sinus tachycardia and left axis deviation.

Laboratory studies showed the hemoglobin concentration to be 11.? Gm. per 100 ml. of blood. The total leukocyte count was 9,650 per cubic millimeter of blood. The pH of the urine was 5 and the specific gravity was 1.004. Glycosuria and proteinuria were absent. Microscopic examination of the urine revealed no formed elements. The patient was placed on a regimen of bed rest and a low-sodium diet and was given 2 ml. of Thiomerin intramuscularly. Digitalization was accomplished by the administration of Acylanid.

The patient's condition gradually improved on this program and she was discharged after 15 days of hospitalization.

The patient was readmitted 5 days later because of aching pain across the shoulders. The results of the physical examination and the electrocardiographic features were essentially like those of the first admission. The erythrocyte sedimentation rate (Westergren) was 106 mm. in 1 hour. The antistreptolysin titer of the serum was at a normal level, being 12 Todd units. The report on a specimen of stool sent to the Minnesota State Board of Public Health was: no virus isolated. The level of urea nitrogen in the blood was 17 mg. per 100 ml. of blood. Three blood cultures, both aerobic and anaerobic, remained sterile. The test for the lupus erythematosus cell and latex flocculation test ga

From the Departments of Medicine and Pathology, The Charles T. Miller Hospital, St. Paul, Minn., and the Departments of Medicine, Radiology, and Pathology, University of Minnesota, Minneapolis, Minn.

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*Address: Department of Pathology, The Charles T. Miller Hospital, 125 West College Ave., St. Paul 2, Minn.

negative results The value for protein bound iodine was 9 2 mg /100 ml of serum The antideoxyribonuclease titer in the serum was normal Cold agglutinins were absent Complement fixation tests for psittacosis influenza A and B and adenovirus gave negative results The venous pressure was 14 cm of water the circulation time was 25 seconds (arm to tongue) and the vital capacity was 1 5 liters

The patient developed increasing dyspnea and nausea Digitalis was withheld for 3 days The pulse rate remained at 120 After 17 days of hospitalization spontaneous labor developed and without difficulty the patient was delivered of a full term infant

The patient course was then stable for the next 10 days after which increasing dyspnea and orthopnea and pain in the right upper quadrant of the abdomen developed Tachycardia persisted The systolic blood pressure measured 90 mm Hg and the diastolic 60 mm Hg The heart was enlarged to the left anterior axillary line and a Grade 2 to 3 systolic murmur was heard along the left sternal border A gallop rhythm developed while the pulmonary field remained clear and the liver enlarged to about 5 cm below the right costal margin The patient condition showed increasing deterioration and he died 16 days after delivery

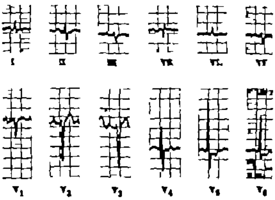


Fig 1 Electrocardiogram recorded during second admission (see text for discussion)

Discussion

DR WINCHELL To summarize this was a 22 year-old woman who developed severe congestive cardiac failure toward the end of the third trimester of her first pregnancy and ultimately died in the post partum period in spite of vigorous medical treatment The differential diagnostic possibilities are numerous One of the first things to be considered is toxemia of pregnancy with hypertension sodium retention and ultimately severe cardiac failure The patient was never hypertensive and gave no evidence of renal impairment in spite of the history of glomerulonephritis at the age of 5 years Without supporting evidence we may rapidly discard toxemia as the cause of the cardiac problem

The most likely cause of failure in a young pregnant patient would be rheumatic disease of the mitral valve Here physical findings give us some help There was on palpation evidence of left ventricular hyperactivity The pulmonic component of the second sound was considerably increased in intensity indicating pulmonary hypertension At the apex there was a systolic murmur which was described as ejection in type but which possibly could have been pansystolic These findings coupled with the history of cardiac failure beginning in the third trimester and becoming more severe in the immediate postpartal period make a fair case for rheumatic mitral reflux In addition to valvular disease one would also have to consider strongly the possibility of recurrent rheumatic myocarditis We get little help from the laboratory however since the antistreptolysin and the more specific antideoxyribonuclease titers were not raised In spite of this we cannot exclude rheumatic carditis

Another area which we should explore is congenital cardiac disease Our comments should be restricted to the acyanotic types since the patient was not cyanotic There was no clinical evidence of pulmonary stenosis atrial septal defect or left sided congenital valvular disease Moreover most types of acyanotic cardiac disease commonly seen in adults are compatible with a normal pregnancy I think that on the basis of the information already available we can rule out congenital lesions of the ordinary types

The possibility of myocarditis should also be considered in this case Instances of viral or nonspecific myocarditis occur developing fortuitously during the latter half of pregnancy and terminating fatally Although the results of viral studies performed in this patient were negative the possibility of a viral myocarditis cannot be excluded

The possibility of idiopathic myocardiopathy either of a familial or nonfamilial sort should also be raised With no positive family history the former would seem

unlikely but a nonfamilial type could not be excluded

Another diagnosis to be considered is that of the myocardiopathy or myocardiosis of pregnancy. In this condition the patient usually develops congestive cardiac failure, tachycardia, and anginoid thoracic pain in the last trimester or more commonly in the immediate or late post partal period.[1] Often in such patients necropsy reveals subendocardial fibrosis and necrosis as well as endocardial thickening with mural thrombi frequently adherent to the thickened endocardium. Embolization is quite frequent in this disorder. This entity, if it is an entity, is thought by some to be caused by pregnancy itself in some yet unknown fashion.[1]

Lastly, we must always consider atherosclerotic cardiac disease with myocardial infarction or fibrosis and failure secondary to this. I place this problem last on our list of differential diagnoses because I think that it is by far the least likely. Myocardial infarction in pregnant young women occurs sporadically, but the incidence of coronary arterial disease in young women with functioning ovaries is very low. I mention this possibility for the sake of completeness and I anticipate that it will get no support from the electrocardiogram. We might now review the electrocardiogram (Fig. 1).

The electrocardiogram shows definite left axis deviation of the QRS complex in the frontal plane. There is no intraventricular conduction defect, and there are ST-T changes in the precordial leads compatible with the results of administration of digitalis. The P waves in Leads II, V_1, and V_2 are strongly suggestive of P mitrale. This electrocardiogram is rather interesting. The P mitrale would suggest left atrial enlargement and may be seen not only in cases of rheumatic mitral valvular disease but in any disorder that leads to increased resistance to filling of the left ventricle, such as systemic hypertension with left ventricular hypertrophy. However, we do not see a pattern of left ventricular hypertrophy. Left axis deviation in a young woman is also an uncommon and, I think, on the basis of the recent literature, an ominous finding. Strong correlation has been shown between true left axis deviation and significant myocardial disease.[3] Even in cases of pure and rather severe mitral reflux, left axis deviation is not very common. In most patients the mean QRS axis in the frontal plane is either normal or tends toward the right. The electrocardiogram then would be compatible with either mitral valvular disease or primary disease of the left ventricle. Dr. Amplatz, may we see the roentgenograms next (Fig. 2).

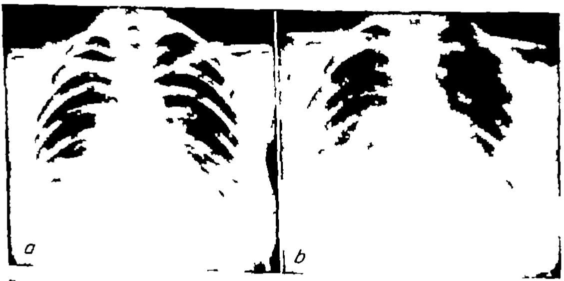


Fig. [illegible] Thoracic roentgenograms made during first admission ( ) and during second admission (b). See text for discussion.

DR AMPLATZ A thoracic roentgenogram taken during the first admission on April 9 1964 shows marked cardiomegaly There is enlargement of the left atrial appendage and a left atrial double density is present No valvular calcification is apparent There is marked pulmonary congestion Kerley's B lines are also present There is a right pleural effusion A second study done on May 11 1964 shows an increased degree of cardiac enlargement Fluid has now appeared at both bases The other findings are unchanged The findings would be compatible with congestive cardiac failure on the basis of mitral reflux or myocardiopathy

DR WINCHELL Dr Amplatz do you see any suggestion of pericardial fluid?

DR AMPLATZ The left atrial enlargement pulmonary congestion and pleural effusion would suggest a failing cardiac muscle rather than pericardial fluid but the latter possibility cannot definitely be excluded by these films

DR WINCHELL I think that we can eliminate toxemia of pregnancy and coronary arterial disease as reasonable possibilities This leaves us with three possible choices (1) rheumatic cardiac disease with predominant mitral reflux and possibly rheumatic active carditis (2) a nonspecific myocarditis occurring fortuitously during pregnancy and (3) the so-called myocardiopathy of pregnancy The left atrial enlargement in the roentgenograms as well as the P mitrale in the electrocardiogram and the physical findings of a probable pansystolic murmur would certainly be strongly suggestive of significant mitral reflux However whether the mitral reflux is secondary or primary cannot be decided with any certainty from the information available I would feel more certain of primary mitral valvular disease if an opening snap and a mitral rumble were present On the other hand the findings would be perfectly compatible with a nonspecific myocarditis occurring during late pregnancy Certainly one does not have to stretch one's imagination to postulate myocarditis with subsequent dilatation of the left ventricle and of the mitral orifice as a cause of mitral reflux In view of the lack of a history of previous rheumatic fever and because of the electrocardiographic findings I would have to choose a form of primary myocardial disease as the most likely cause of the patient's problem I cannot exclude the myocardiopathy of pregnancy The patient however was not Negro and the rarity of the entity itself combined with its racial predilection would make it an extremely unlikely possibility [1] My final diagnosis will therefore be myocarditis of unknown cause occurring late in pregnancy with rheumatic mitral reflux and/or myocarditis as a close second choice

DR SPECKHALS Thank you Dr Winchell Dr Edwards would you now present the pathologic findings

DR EDWARDS The main pathologic findings were confined to the heart lungs and liver The heart was slightly enlarged weighing 345 grams The right ventricle was considerably dilated but not thickened the wall measured 5 mm in thickness The left ventricle was also somewhat dilated although not nearly so much as the right and its wall showed slight hypertrophy measuring 1 6 cm in thickness The left atrium was also moderately enlarged and the wall was somewhat thickened The most striking finding in the heart was diffuse thickening of the endocardium of all chambers particularly of the left ventricle giving the mural endocardium a pearly white appearance (Fig 3) The anterior and posterior leaflets of the mitral valve were thickened and the edges of the anterior leaflet were rolled inward There were two small clefts in the anterior leaflet but chordae tendineae supported the edges of the clefts The other valves were not remarkable and there were no other defects in the heart The coronary arteries were normal The liver was enlarged and showed the typical nutmeg appearance of chronic passive congestion The lungs had obvious areas of infarction in the right upper and middle lobes A moderate amount of pulmonary edema was also present

Histologic examination of sections taken from several areas in the left ventricle showed the endocardium to be thickened to the degree that this layer measured up to 1 5 mm The thickening was caused by deposits of collagenous and elastic fibers as well as by bundles of hypertrophied

muscle (Fig. 4). The process of endocardial thickening extended into the intratrabecular sinusoids (Fig. 4). The myocardium was normal in each of the many sections examined. Histologic examination of the lungs showed atelectasis, edema, and hemosiderosis. Medial thickening of the walls of the pulmonary veins (Fig. 5 *a*) as well as medial thickening of the walls of the muscular pulmonary arteries (Fig. 5 *b*) were present in moderate degrees. Intimal proliferation was seen in arterioles and in venules (Fig. 5 *c*).

The pathologic findings would suggest mitral insufficiency. The anterior leaflet of the mitral valve was thickened and more rigid than usual and, as a result, may not have been able to close properly. In addition, the papillary muscles probably exerted undue tension on the valve during ventricular systole because of their being pulled away from the valve by the dilatation of the left ventricle. Also, minor degrees of regurgitation might have occurred through the clefts in the anterior leaflet.

The pulmonary vascular changes are also of some interest in that beside the changes of acute congestion they show evidence of a long-standing increase in pulmonary venous pressure. One would have to conclude that the patient had had pulmonary venous hypertension for some time prior to the apparent clinical onset of the disease.

The lack of histologic abnormalities in the myocardium and the obvious cardiac failure in this patient is not an unusual phenomenon. In many instances of myocardiopathy, no histologic abnormalities can be discovered with light microscopy even with the aid of special stains. It should be pointed out, however, that the histologic findings do not support a diagnosis of an acute myocarditis.

The question arises whether the fibroelastosis which was striking was a primary or secondary problem or, more pointedly, whether this was a case of congenital endocardial fibroelastosis surviving to adulthood. From the appearance of the heart this seems unlikely. There was relatively minimal hypertrophy of the left ventricle in contrast to the marked hypertrophy seen in cases in which the endocardial fibroelastosis seems clearly to be of congenital origin. I would favor the view that in this case the endocardial fibroelastosis was secondary to the effects



Fig. 3. Gross specimen of heart. *a*, Left atrium and left ventricle. Mild left ventricular hypertrophy. The endocardium of the atrium and the ventricle is grossly thickened, giving an opaque pale appearance. In the anterior leaflet of the mitral valve there are two clefts (*arrows*). The edges of the clefts are supported by chordae. *b*, Left ventricle and opened aortic valve. The aortic valve is normal. The endocardium of the left ventricle is thickened. The endocardial thickening in the myocardial sinusoids is also evident.

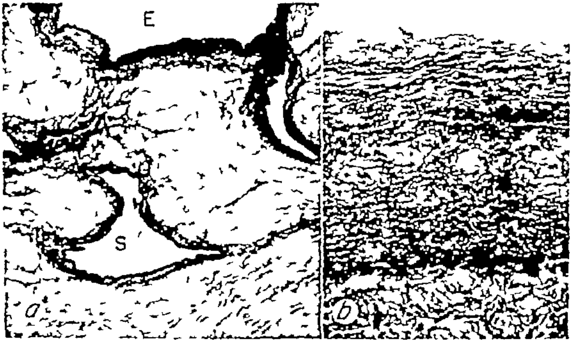


Fig. 4. Photomicrographs of left ventricular wall. *a*, The endocardium (*E*) is grossly thickened, as are the endocardial linings of the adjacent myocardial sinusoids (*S*). Elastic tissue stain. ×20. *b*, High power view of endocardium of left ventricle. Two layers of collagenous and elastic tissue thickening are evident. Between these two is a layer of bundles of hypertrophied smooth muscle cells. Elastic tissue stain. ×80.

of myocardial failure. Dr. From, you have reviewed a considerable amount of the literature on adult endocardial fibroelastosis and on the myocarditis of pregnancy. Would you please comment on these entities in the light of existing literature.

DR. FROM. Endocardial fibroelastosis (EFE) is not uncommon in adults. The distribution, however, is usually patchy and related to common clinical entities. One of the most common causes of EFE is myocardial infarction. In this situation the endocardium is thickened where it overlies areas of healed myocardial infarction.[4] Another common cause of EFE in adults is rheumatic cardiac disease with secondary valvular reflux. The so-called jet lesions may be considered to be examples of localized EFE.[4] Another interesting entity is the endomyocardial fibrosis seen in Africa, in which there is diffuse and patchy fibrosis of the endocardium and of the myocardium.[5] The etiology of this entity is unknown. Another disease in which there may be marked thickening of the endocardium is the myocarditis of pregnancy. In this situation, in addition to endocardial thickening and mural thrombi, there is usually a marked fibrotic and inflammatory reaction in the subendocardial myocardium.[1] Another group of patients who inconstantly demonstrate diffusely thickened endocardium, especially of the left ventricle, are those with chronic cardiac failure and marked ventricular dilatation. EFE is also associated with numerous types of congenital cardiac malformations.[7] In such cases the endocardial thickening may be related to the abnormal stresses placed upon the affected chamber by the malformation.[7] Lastly, there are patients with endocardial thickening in whom the myocardium is histologically normal, as in the case presented here. There is no evidence of coronary arterial disease, and it is in this group that the pathology is most similar to the congenital form of EFE.

Many theories have been advanced to explain the genesis of EFE, but none has been completely satisfactory. Myocardial and endocardial hypoxia has been suggested as a possible etiology by Johnson.[8] The frequent presence of viable smooth muscle cells in the thickened endocardium itself, however, refutes this suggestion.[9]

Others have discussed the occurrence of primary inflammatory processes involving the endocardium alone or both the endocardium and the myocardium and causing secondary EFE.[18] The suggestion of Still and Boult[11] on the basis of electron microscopy is that deposits of fibrin on the endocardial surface become incorporated into the endocardium with resultant thickening. Recently, Miller and associates[12] have shown EFE to develop in dogs after the lymphatic drainage of the heart was obstructed. The endocardial thickening occurred in the absence of clinical cardiac failure or ventricular dilatation. These authors suggested that there may be a relationship between the experimental disease and the human disease.[12] As yet it is to be seen whether their observations will receive confirmation by others. At the present time Black-Schaffer's suggestions have received the most experimental support.[8] He considers that all EFE is a secondary rather than a primary process and that the primary fault in almost all of the various forms of EFE is underlying myocardial weakness, either generalized or localized. A weakened or failing heart has a tendency to dilate, and the tension of the ventricular wall increases for any given intraluminal pressure as the radius increases according to the law



Fig. 5. Photomicrographs of pulmonary vessels. a, An intrapulmonary vein. There is medial hypertrophy considered to be indicative of chronic pulmonary venous hypertension. Elastic tissue stain. X5[illegible]. b, A muscular artery and an arteriolar branch. Each segment shows medial hypertrophy. Elastic tissue stain. X8[illegible]. c, A pulmonary arteriole or venule. The intima is grossly thickened with fibrous tissue, causing the lumen to be markedly narrowed. Elastic tissue stain. X550.

of Laplace Black Schaffer would envision endocardial thickening as a response to the increasing diastolic endocardial tension as the heart dilates Support for his suggestion comes from evidence that physical forces may stimulate the development of the elastic tissue[14] The vast differences in the amount of endocardial thickening in patients with the various types of cardiac failure might be ascribed to individual variation in the ability to bring forth a specific connective tissue response comparable to the individual variation in the ability to form keloid The adult patient with myocardiopathy and EFE may be an endocardial keloid former

Because there are so many postulated causes of EFE it is obvious that much more work will have to be done before one can present a secure etiological classification of the progress Moreover since the heart has a relatively limited pattern of response to a large and diverse number of possible agents or processes the identification of definite cause and-effect relationships will require the development of methods of analyses which go beyond light and electron microscopy

The question whether there is a specific myocardiopathy associated with and caused by pregnancy is a difficult one As has already been mentioned there are some who favor the view that such an entity exists[1] and others who think that it does not exist[2] As Benchimol and his associates[15] have pointed out however most patients with cardiac failure in pregnancy if carefully analyzed can be placed in a standard diagnostic category without resort to the creation of a specific entity peculiar to pregnancy alone

In summary then I think that our patient represents a case of myocardiopathy of undetermined cause with secondary EFE and secondary mitral reflux Because the pathologic findings indicate long standing left ventricular dysfunction I think that the problem was not related to pregnancy in any way other than that the cardiovascular stresses of pregnancy forced an already weakened heart into complete decompensation

Diagnosis Idiopathic myocardiopathy with endocardial fibroelastosis occurring during pregnancy

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Fundamentals of clinical cardiology

Mitral stenosis

Hemodynamic, electrocardiographic, and vectorcardiographic studies

*Yu Chen Lee, M.D.**
*Leonard Scherlis, M.D.***
*Robert T. Singleton, M.D.****
Baltimore, Md.

As experience has accumulated in the evaluation of patients with mitral stenosis, conflicting data have been reported in regard to the correlation of electrocardiographic and vectorcardiographic evidence of right ventricular hypertrophy and right ventricular pressure in pure mitral stenosis.

Good correlation has been demonstrated by some investigators,[1-4] whereas others have reported that the correlation of hemodynamic and electrocardiographic and vectorcardiographic features of mitral stenosis is variable.[5-7] There is also disagreement in regard to the value of the left atrial pressure curve for differentiating mitral stenosis from mitral insufficiency.[8-12] In the present study of 75 patients, electrocardiographic, vectorcardiographic, and hemodynamic data are reported in order to evaluate their usefulness in determining the severity of mitral stenosis.

Material and methods

This study includes 75 patients observed at the University of Maryland Hospital in whom evidence for a significant degree of mitral stenosis was demonstrated by transseptal left heart catheterization. Right heart catheterization was also performed in each instance. Excluded from this study were patients who had a significant degree of mitral insufficiency or aortic valvular involvement. Cineangiocardiography was performed in doubtful cases in order to exclude significant mitral insufficiency. In 63 patients in whom mitral commissurotomy was performed, the preoperative diagnosis of mitral stenosis with minimal or no mitral regurgitation was confirmed. Electrocardiograms including 12 conventional leads and Lead V_{3R} and vectorcardiograms were recorded utilizing the cube reference system of electrode placement.[13] In 34 patients, phonocardiograms were recorded with a Sanborn Twin Beam photographic instrument with a simultaneous electrocardiogram for time reference. The electrocardiographic and vectorcardiographic diagnosis of ventricular hypertrophy was based on the various criteria summarized in our previous report.[14] There were 57 females and 18 males ranging in age from 18 to 70 years. The age distribution is shown in Table I.

Results

Hemodynamic data. The mean left atrial pressure was less than 20 mm. Hg in 28, 20 to 30 mm. Hg in 34, and more than 30

From the Division of Cardiology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Md.
Received for publication Oct. 16, 1964.
*Assistant Professor of Medicine.
**Associate Professor of Medicine; Head, Division of Cardiology.
***Assistant Professor of Medicine; Co-Director, Cardiovascular Laboratory.

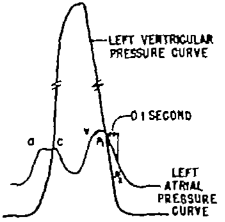


Fig. 1. The left atrial pressure curve is superimposed on the left ventricular pressure curves. P_1 is the point at which the left ventricular pressure curve crosses the left atrial pressure curve and indicates the time of the opening of the mitral valve. P_2 is the left atrial pressure 0.10 sec. after P_1. *MLAP* is mean left atrial pressure.

mm. Hg in 13. The analysis of the slope of the left atrial decompression curve (y wave) revealed prolonged emptying of the left atrium. The rate of the y descent in the first tenth of a second after the opening of the mitral valve was measured and then divided by the mean left atrial pressure. The formula used (Fig. 1) was

P_1 P MLAP

where P_1 is left atrial pressure at the time of the opening of the mitral valve, P_2 is left atrial pressure 0.10 second after the opening of the mitral valve, and MLAP is mean left atrial pressure.

The value of the ratio was 0.3 or less in the absence of tachycardia. In the presence of tachycardia the duration of the y descent may be too short for measurement. There were 3 such instances. No significant differences were found between those patients with normal sinus rhythm and those with atrial fibrillation (Fig. 2). The left ventricular pressure was less than 140 mm. Hg in all but one patient, in whom the left ventricular systolic pressure was 170 mm. Hg. The resting right ventricular systolic pressure was less than 30 mm. Hg in 3 patients, 30 to 50 mm. Hg in 42, and 51 to 120 mm. Hg in 30. Those with normal or slightly elevated right ventricular systolic pressures at rest had a significant elevation of pressure after exercise. There was a poor relationship between the mean left atrial pressure and the right ventricular systolic pressure (Fig. 3).

Electrocardiograms. Atrial fibrillation was present in 34 patients and normal sinus rhythm in 41. P wave enlargement was noted in 34 patients, and the P-R interval was prolonged in 6. The QRS duration was less than 0.10 second in 71, 0.10 second in 3, and 0.12 second in 1. The QRS configuration in Lead V_1 is shown in Table II.

The height of the R wave in Lead V_1 was equal to or greater than 5 mm. in 12 patients. The frontal QRS axis was between 0 and +150 degrees in all but 2 patients (Fig. 4). In 37 patients there was no evidence of ventricular hypertrophy. There was right ventricular hypertrophy in 26 patients, left ventricular hypertrophy in 6, and combined ventricular hypertrophy in 3. Two had evidence of anteroseptal myocardial infarction, and 1 had right bundle branch block.

Vectorcardiograms. Twenty-eight records revealed no evidence of ventricular hypertrophy. Twenty demonstrated right ventricular hypertrophy, 11 right ventricular preponderance, 9 left ventricular hypertrophy, 5 combined ventricular hypertrophy, 1 anteroseptal myocardial infarction, and 1 right bundle branch block.

Right ventricular hypertrophy was divided into three general groups characterized by an increasing degree of displacement of the QRSsÊ loop anteriorly and to the right[14] (Figs. 5-7). In the vectorcardiograms classified as showing right ventricular preponderance, the direction of inscription of the QRSsÊ loop in the horizontal projection was counterclockwise

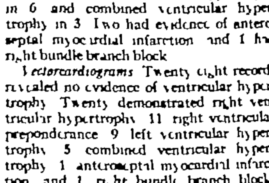


Fig. 2. Note the slow runoff of the left atrial pressure curve. ECG reveals atrial fibrillation.

Table I Age distribution of patients

Age (yr)	Number
18–20	2
21–30	8
31–40	23
41–50	1
51–60	18
61–70	3

Table II QRS configuration in V_1

Configuration	Number
rS (rs)	54
r	1
rsR	4
R	1
rS (Rs)	6
qr	3
qR	1
q	1
QS	4

and in the sagittal projection it was clockwise (Fig. 6). In both projections the QRSsÊ loop was displaced more anteriorly than normal. In the frontal projection the direction of inscription of the QRSsÊ loop was either clockwise or counterclockwise and no left axis deviation was seen. An example of a vectorcardiogram which was classified as showing left ventricular hypertrophy is shown in Fig. 9.

The vectorcardiogram revealed right ventricular hypertrophy in 8 instances with the electrocardiogram showing no definite evidence of right ventricular hypertrophy. In 3 cases the electrocardiogram manifested right ventricular hypertrophy which could not be detected by the vectorcardiogram. Forty-one patients had no electrocardiographic or vectorcardiographic evidence of isolated right ventricular hypertrophy.

CORRELATION OF HEMODYNAMIC DATA WITH ELECTROCARDIOGRAM AND VECTORCARDIOGRAM

A. Electrocardiographic or vectorcardiographic evidence of right ventricular hypertrophy (34 patients). The average age was 44 years ranging from 18 to 22 years. The average right ventricular systolic pressure was 60 mm Hg with a range from 30 to 120 mm Hg. The average mean left atrial pressure was 24 mm Hg ranging from 14 to 42 mm Hg. Twenty one patients had atrial fibrillation. Among the 31 patients who had vectorcardiographic evidence of right ventricular hypertrophy the average right ventricular systolic pressure was correlated with the type of right ventricular hypertrophy as follows: right ventricular hypertrophy type 3—(6 patients) 76 mm Hg; right ventricular hypertrophy type 2—(8 patients) 75 mm Hg; right ventricular hypertrophy type 1—(6 patients) 43 mm Hg; right ventricular preponderance—(11 patients) 55 mm Hg.

B. No electrocardiographic or vectorcardiographic evidence of ventricular hypertrophy (25 patients). The average age was 42 years ranging from 23 to 70 years. The average right ventricular systolic pressure was 43 mm Hg with a range from 24 to 70 mm Hg. The average mean left atrial pressure was 23 mm Hg rang-

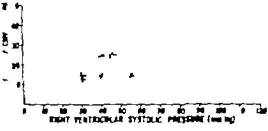


Fig. 3 The relationship of the mean left atrial pressure and the right ventricular systolic pressure

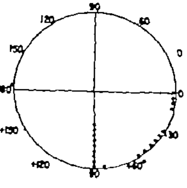
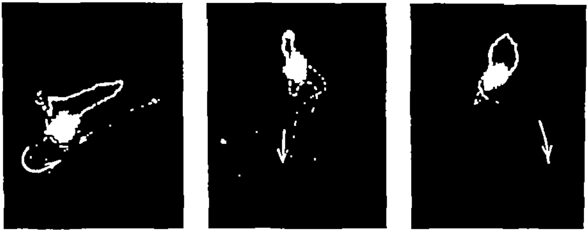


Fig. 4 Mean frontal QRS axis



H S F

Fig. 5. Fifty-six-years-old. MLAP 28 mm. Hg; LV pressure 132 mm. Hg; RV pressure 70 mm. Hg. The vectorcardiogram represents type 1 RVH. The initial inscription of the QRS Ē loop is directed to the right and anteriorly and then to the left. The returning loop turns abruptly to the right and crosses the centrifugal loop before returning to the E point in the horizontal plane.

ing from 12 to 32 mm. Hg. Six of the patients had atrial fibrillation.

C. Electrocardiographic or vectorcardiographic evidence of left ventricular hypertrophy (9 patients). The average age was 42 years, ranging from 30 to 61 years. The average right ventricular systolic pressure was 47 mm. Hg, with a range from 35 to 70 mm. Hg. The average mean left atrial pressure was 20 mm. Hg, ranging from 12 to 35 mm. Hg. Three of the patients had atrial fibrillation.

Phonocardiograms.—Phonocardiograms were available in 54 patients. The time interval between the onset of the QRS of the electrocardiogram and the onset of the maximal vibrations of the first heart sound (Q-1) and the interval between the beginning of the second heart sound and the beginning of the opening snap (2-O.S.) were measured. In each patient the average of at least 10 cycles was used to determine the Q-1 and 2-O.S. intervals. An opening snap was present in 44 patients. Q-1 ranged from 0.07 to 0.12 second and 2-O.S. ranged from 0.06 to 0.12 second.

There was no close correlation of the Q-1 or 2-O.S. interval with either the right ventricular systolic pressure or the mean left atrial pressure (Fig. 10). However, the Q-1 minus 2-O.S. was equal to or more than 0 in all but 7 patients.

Discussion

Although left atrial pressure tracings are widely used in assessing mitral valvular involvement, there are no uniform criteria on the interpretation of the data obtained or their value in assessing the severity of mitral insufficiency and/or mitral stenosis. The measurement of the rate of the "y" descent in the first tenth of a second from the peak of the "v" wave was considered by Morrow and associates[9] and by Neustadt and Shaffer[10] to be valuable for differentiating predominant mitral stenosis from predominant mitral insufficiency. Nixon[11] pointed out that the left atrial "v" peak does not seem to coincide with the time of opening of the mitral valve. He stated that conclusions based on the measurement of the first 0.1 second of the "y" descent are not correct, and that the interpretation of the left atrial pressure pulses is therefore not so simple as this basic measurement suggests.

Nakanishi[12] concluded that the left atrial pressure pulse in mitral stenosis simulates that in mitral regurgitation when atrial fibrillation is present.

The mitral valve usually opens 0.01 to 0.06 second after the peak of the "v" wave. In the present study, the attempt was made to use the time of the opening of the mitral valve and the first 0.1 second of the

y descent of the v wave after the opening rather than the peak of the v wave. The left ventricular pressure tracing was superimposed on the left atrial pressure tracing in order to determine the approximate time of opening of the mitral valve. This technique is not so accurate in the presence of atrial fibrillation. Patients with tachycardia may not have a sufficiently long y descent to allow adequate measurement. However, the presence of a significant diastolic gradient is helpful in these instances in assessing the severity of mitral stenosis.

In the absence of tachycardia, calculation of the formula P_1 P /MLAP has been helpful in differentiating predominant mitral stenosis from predominant mitral insufficiency. The value is equal to or less than 0.3 among patients who have predominant mitral stenosis.

In the 54 patients in whom phonocardiograms were available, the Q-1 and 2-OS intervals did not correlate well with the

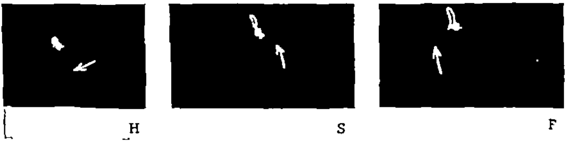


Fig. 6. Forty-eight years old. MLAP 22 mm. Hg. LV pressure 125 mm. Hg. RV pressure 100 mm. Hg. The vectorcardiogram represents type 2 RVH. After the centrifugal inscription to the left, the QRS-Ê loop is then inscribed in a clockwise direction anteriorly and to the right in the horizontal plane.

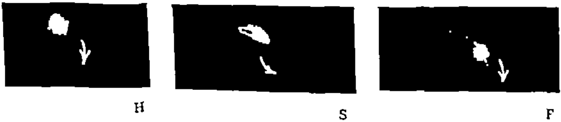


Fig. 7. Fifty-two years old. MLAP 18 mm. Hg. LV pressure 130 mm. Hg. RV pressure 75 mm. Hg. The vectorcardiogram represents type 3 RVH. In the horizontal plane, the initial portion of the QRS-Ê loop is directed almost immediately to the left with a small or absent septal deflection. It is then quickly inscribed to the right and anteriorly in a clockwise direction. The main portion of the QRS-Ê loop is displaced to the right and anteriorly.

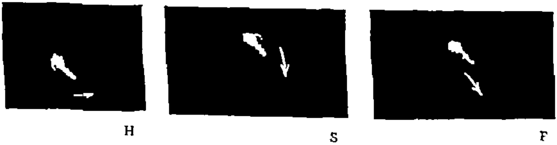
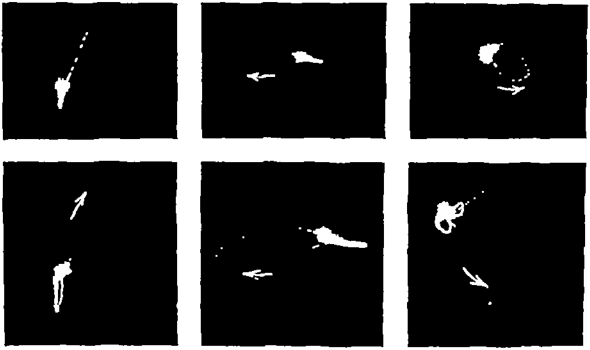


Fig. 8. Forty-two years old. MLAP 15 mm. Hg. RV pressure 55 mm. Hg. The vectorcardiogram represents right ventricular preponderance.



H S F

Fig. 9. Forty-five-year-old. MLAP 35 mm. Hg. LV pressure 114 mm. Hg. RV pressure 71 mm. Hg. The vectorcardiogram revealed posterior displacement of the QRS-Ê loop in the horizontal and sagittal planes. The direction of inscription of the frontal plane is counterclockwise. The T loop is opposite of the QRS-Ê loop.

degree of right ventricular pressure or mean left atrial pressure.

However, in every instance the Q-1 exceeded the upper limit of normal usually given (0.06 second), ranging from 0.07 to 0.13 second. The 2-O.S. interval ranged from 0.06 to 0.12 second.

It is significant that in all but 7 patients the Q-1 minus 2-O.S. was equal to or greater than 0. This is an agreement with the result of Wells[9] who stated that if the Q-1 minus 2-O.S. is over −1 there is probably severe mitral stenosis.

In the present study there was fairly good agreement between the electrocardiogram and vectorcardiogram. When both manifested right ventricular hypertrophy there was a significant elevation of the right ventricular systolic pressure. Types 2 and 3 right ventricular hypertrophy were associated with higher right ventricular systolic pressures than was type 1.

In contrast to the findings with such lesions as congenital pulmonary stenosis or atrial septal defect, the incidence of tall R waves in the right precordial leads in mitral stenosis proved to be quite low. Both the electrocardiogram and vectorcardiogram lacked evidence of right ventricular hypertrophy in 15 patients with mitral stenosis despite elevated resting right ventricular pressures. Cosby and associates[3] stated that in mitral stenosis normal or borderline electrocardiograms appeared frequently up to a mean right ventricular pressure level of 60 mm. Hg. Since the left ventricle is far more predominant electrically in adults, the load

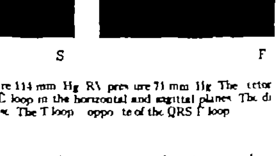


Fig. 10. The relationship of mean left atrial pressure to the Q-1 and 2-O.S. interval.

of the right ventricle may not have increased to the point at which the balance of electrical forces became sufficiently altered in those patients to produce electrical evidence of right ventricular hypertrophy

It is well known that electrocardiographic evidence of left ventricular hypertrophy can exist in the presence of mitral stenosis [4, 16, 17]

There were 9 patients in the present series who had posterior displacement of the QRSsÊ loop one of the features of left ventricular hypertrophy In one patient the left ventricular pressure was 170 mm Hg One patient had a left ventricular systolic pressure of 140 mm Hg and a past history of significant hypertension with casual readings as high as 200/120 mm Hg The left ventricular hypertrophy in these 2 patients may be explained by systemic hypertension

Previous investigators reported that systemic hypertension is frequently found in cases of mitral stenosis [16, 17] They stated that the clinical and electrocardiographic signs of mitral stenosis were modified by the left ventricular hypertrophy However there is no satisfactory explanation for the electrocardiographic evidence of left ventricular hypertrophy in the presence of pure mitral stenosis as an isolated cardiovascular lesion

Some investigators[13] have attributed the posterior displacement of the QRSsÊ loop in mitral stenosis to the concomitant pulmonary emphysema One of the 9 patients with left ventricular preponderance had clinical evidence of emphysema However pulmonary emphysema was present in patients with electrocardiographic or vectorcardiographic evidence of right ventricular hypertrophy

Since rheumatic heart disease involves not only the valve but also the myocardium fibrosis of the myocardium or conducting system may presumably alter the balance of electrical forces thus producing otherwise unexpected posterior displacement of the QRSsÊ loop in the patients with mitral stenosis

Further studies are needed to elucidate the mechanism of the peculiar posterior displacement of the QRSsÊ loop in the patients with mitral stenosis

Summary

The data of transseptal left heart and right heart catheterization were correlated with the phonocardiographic electrocardiographic and vectorcardiographic findings in 75 patients with significant mitral stenosis Measurement of the rate of the y descent in the first tenth of a second after the opening of the mitral valve was helpful in detecting the presence of significant mitral stenosis In the absence of tachycardia the value of the formula $P_1 P_2$/MLAP was 0 3 or less among patients who had predominant mitral stenosis No significant difference was seen between patients with normal sinus rhythm and those with atrial fibrillation In the 54 available phonocardiograms Q 1 minus 2 O S was equal to or greater than 0 in all but 7 patients The electrocardiograms revealed evidence of right ventricular hypertrophy in 26 instances whereas the vectorcardiograms revealed evidence of right ventricular hypertrophy in 31 instances Forty-one patients had neither electrocardiographic nor vectorcardiographic evidence of isolated right ventricular hypertrophy Both the electrocardiogram and vectorcardiogram failed to show patterns typical of right ventricular hypertrophy in 15 patients despite the significantly elevated resting right ventricular pressure There were 9 patients who had posterior displacement of the QRSsÊ loop

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Cardiovascular actions of narcotic analgesics

*Henry W Elliott M D Ph D**
*M Adam Abdel Rahman Ph D***
San Francisco Calif

Statements to the effect that the usual doses of morphine or morphine like analgesics have minimal effects on the cardiovascular system of man can be found in textbooks of pharmacology There is however extensive evidence of the circulatory effects of these drugs

The most notable effect of narcotics on the cardiovascular system is hypotension which has been observed in man and the usual experimental animals Physicians who have occasion to observe the effects of narcotics as used in preanesthetic medication are never surprised to find the preanesthetic blood pressure lower than that recorded on the ward Of course this is not invariably true and even when it does happen it may be the result of sedation or tranquilization

In normal man the cardiovascular effects of narcotic analgesics are minimal thus in healthy subjects stress must be placed on the circulation to make the actions obvious enough to be sure of their existence or to permit a comparison of drugs Gravity has been utilized as a stress in the tilt table test By this technique it has been demonstrated that 12 to 30 mg of morphine intramuscularly significantly increased the incidence of hypotension and fainting in subjects tilted 75 degrees to the head up position The effect was largely reversed by wrapping the legs which indicates orthostatic hypotension due to peripheral pooling of blood Similar results have subsequently been reported for other narcotics and narcotic antagonists and the test continues to be used to evaluate the circulatory effects of analgesics The effects of repeated injections of narcotics have not been reported possibly because of the demanding nature of the test but acute tolerance to the circulatory effects would be expected as observed when the drugs are used repeatedly as in anesthesia

The orthostatic hypotension could be the result of direct depression of either the peripheral vessels the vasomotor center or the myocardium or a combination of these Here evidence from human studies is meager and it is difficult to extrapolate animal evidence to man because of species differences Thus in the dog a direct peripheral action of morphine has been reported by some workers which could be the result of histamine release However others believe that a central action of morphine is more important in the dog and in the cat both a central effect and the release of histamine have been implicated In the rat the hypotension that follows narcotics is apparently due pri

From the Department of Pharmacology and Experimental Therapeutics University of California San Francisco Medical Center San Francisco Calif

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*Professor of Pharmacology University of California San Francisco Medical Center San Francisco Calif 94122
**Lecturer in Pharmacology Faculty

marily to peripheral vagal stimulation (Bezold Jarisch effect). Thus since narcotic analgesics are histamine liberators in man as evidenced by the formation of wheals and pseudopods after intracutaneous injection, it is tempting to ascribe their hypotensive effects in man to the release of histamine, but it is more prudent to assume, until more evidence is available, that both peripheral and central actions may be involved. There is little evidence to implicate myocardial depression, although the observation that methadone was much more toxic than morphine and meperidine to the isolated rabbit heart engendered warnings against the intravenous use of methadone.

Other cardiovascular actions are relatively unimportant. Heart rate tends to increase and cardiac output is usually unchanged. Cerebral blood flow may be increased indirectly as a result of the retention of CO_2, and renal blood flow may be decreased, possibly because of the release of an antidiuretic hormone.

Since the production of orthostatic hypotension appears to be the principal cardiovascular effect of the narcotic analgesics, warnings to use these drugs with caution in hypovolemic states seem to be justified. Their beneficial effects in shock accompanied by pain will, however, usually take precedence, but the smallest dose required to control pain should be the optimal dose. Again, in patients with myocardial infarction the relief of pain and dyspnea by narcotics indirectly increases the efficiency of the heart by improving pulmonary ventilation, decreasing purposeless activity, and reducing cardiac work. These benefits usually outweigh the risk of incurring hypotension or any of the other side effects of narcotics, such as respiratory depression, vomiting and retching, constipation, and the retention of urine. The same holds true in cases of paroxysmal pulmonary edema, in which, according to Altschule, morphine aborts most of the mild and many of the severe attacks. It is said to give the best results in pulmonary edema associated with hypertension, uremia, or mitral stenosis and should be used with caution in patients with pulmonary disease or hypothyroidism because of exaggerated respiratory depression. The mechanism of action of morphine in pulmonary edema is not completely known either; it probably acts centrally as an inhibitor of reflexes involved in the genesis of pulmonary edema and as a respiratory depressant and tranquilizer. Respiratory depression may physically decrease the suction effect of dyspnea, and tranquilization may lower the metabolic rate with consequent decrease in cardiac output and pulmonary arterial pressure. Cardiac output may also be decreased by the peripheral pooling action of narcotics, and this action may predominate and even precipitate collapse if therapy includes use of the sitting position with the legs dependent.

In summary, the cardiovascular actions of morphine, meperidine, methadone, and related drugs are practically equivalent when the drugs are used in equipotent doses, consist mainly of peripheral vasodilation, and do not contraindicate their use when indicated for the symptomatic relief of pain or acute pulmonary edema. This is especially true now that specific narcotic antagonists are available which will reverse the cardiovascular depression as well as the respiratory depression sometimes caused by narcotics. The cardiovascular actions should, however, serve as a reminder that the smallest effective dose is the safest dose and that a higher incidence of hypotension, dizziness, fainting, nausea, and vomiting may be expected in ambulatory patients.

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Annotations

Pulmonary angiography

It seems likely that pulmonary embolic disease will continue to be a leading cause of disability and death so long as sick people are put to bed. Despite a general awareness of the problem, the frightening incidence of pulmonary embolism among elderly, debilitated patients is not really well appreciated. Conversely, an awakened interest has been known to double the frequency with which the diagnosis is made. Even if all patients were ambulated on the second or third day, some embolic disease would still be seen, since it is known to occur even in vigorous, relatively young individuals. It is in this group particularly that the diagnosis of embolism is so vital, since appropriate measures can insure an essentially normal life span despite an otherwise often fatal disorder. To be sure, the likelihood is much greater in aged, enfeebled patients with heart disease, malignancy, or serious injuries. However, it is also more suspect in such cases and the diagnosis is made more often. But here, too, atypical patterns outnumber the classical to a point at which the whole clinical picture of pulmonary embolic disease merits reassessment. One is struck by the fact that simple failure to thrive or to improve under adequate modern therapy from a variety of illnesses may be the only clue to pulmonary embolism. As in the case of bacterial endocarditis and other usually fatal but treatable disorders, the merest hint of the diagnosis should lead to an all-out search.

A clinical impression of pulmonary embolism or infarction may be strengthened by a higher than normal serum LDH paired with normal SGOT. These enzyme determinations also help to differentiate acute pulmonary embolism from myocardial infarction. Additional supporting evidence includes elevated serum bilirubin, important disagreement between the pCO_2 levels of alveolar air and arterial blood, certain electrocardiographic abnormalities, and at times suggestive roentgenograms. These findings, singly or in combination, presently constitute the indications for pulmonary angiography. It may also be done in their absence, however, if there is sufficient clinical provocation. An obvious exception to this general rule is the patient who is overwhelmed by a massive injury and who may not survive the procedure. No specific guidelines can be laid down, however, and decisions must be made on the basis of previous experience. Nevertheless, it must be noted that pulmonary angiography has been performed on desperately ill patients without ill effect or further deterioration.

Pulmonary angiography is presently one of a number of studies used for the identification of embolic disease, and although it is probably the very best one, it must still be interpreted in conjunction with the others. Despite the improved specificity of various inferential tests, none approaches the objectivity of pulmonary angiography. This may demonstrate not only the presence of local block but at times the number, extent, and location of the obstructions. It may help to decide in favor of one therapeutic regimen instead of another. It is of the utmost value, negative as well as positive, when obtained within the first day or two of the acute event. Frank evidence of obstruction of the vessels is not only self-evident but diagnostic in high degree. Conversely, a clear pulmonary vascular tree shown during the first 48 to 72 hours almost certainly rules out the presence of macroemboli and helps direct the investigation on another course. Since lysis of clots begins rather promptly and is well established at 48 hours, the findings become increasingly uncertain after 2 or 3 days and less useful. The pulmonary angiogram does not differentiate embolism from thrombosis and is of limited value in detecting microemboli. Reduction in caliber and sparseness of the terminal vessels suggest occlusion by small emboli, but this is not diagnostic.

Congestive failure and particularly mitral stenosis, disorders associated with elevated pulmonary venous pressures, both interfere with interpretation of the pulmonary angiogram. The high venous pressure initiates reactive arterial vasoconstruction which, probably because of our usually upright posture, involves the lower lobes more than the upper. The normally larger arteries to the lower lobes become smaller than the vessels of the upper lobe, which now carry most of the blood. The resulting appearance is not too greatly unlike that seen with multiple emboli to the lower lobes and is differentiated *from it, if at all,* with difficulty. Unfortunately, pulmonary embolic disease is common in both congestive failure and mitral disease, but since emboli are rarely quite symmetrical, the lower lobes can profitably be compared one with the other. A vascular distortion which sometimes lends to an erroneous diagnosis of pulmonary embolism is isolated vascular compression due to *local* emphysema. Pneumonitis offers no serious problems. Although the parenchymatous opacification may be identical in appearance to that seen with infarct, the vascular tree remains normal in the infected lung.

Pulmonary angiography is accomplished in one of two general ways: the simpler intravenous method is reserved for near moribund patients. It is performed by rapidly injecting 80 to 100 ml. of contrast material into the veins of both arms. Rapid serial x-ray chest films are then obtained by means of a synchronized film changer. Unfortunately, the contrast material is greatly diluted by the time it reaches the lungs so that only gross abnormalities can be identified. Preferably, a side-opening catheter of generous size is introduced into the right ventricle through an arm vein and the superior vena cava. The contrast medium is delivered through it into the outflow tract or just beyond the pulmonary valve by a mechanical injector. This results in dramatic opacification of the arterial tree and filling of the smallest branches in exquisite detail. Roentgenograms are obtained as before. Normally, 12 to 20 films are made, spaced so as to follow the progress of the contrast material through the capillary and venous phases.

In addition to gross obvious obstruction of major vascular channels, a *number of other* abnormalities may be detected which in varying degree indicate pulmonary embolic disease. In complete block may exhibit scalloping or irregularity of the vessel contour conforming probably to the free edge of an adherent retracted or partly lysed embolus. Otherwise inapparent occlusions delay filling of the distal vessels ordinarily supplied by the involved channels. However, this may only be evident by comparison with bordering or contralateral areas. Similarly, opacification once attained in compromised segments persists or pools long after the adjacent lung has cleared. A suspected area may, for example, exhibit arterial opacification when other neighboring divisions are already in the venous phase. Vessels proximal to an obstruction become dilated, whereas those beyond it are narrowed. The main pulmonary trunks may widen extensively in association with elevated pulmonary pressures.

Paired *enzyme determinations* (LDH, SGOT) are presently the best rapid and simple screening test now available for suspected pulmonary embolic disease. Similarly, pulmonary angiography is the most definitive and objective means for confirming the diagnosis. Probably, however, it should not be done as an occasional procedure. When it is performed frequently by an experienced team and the films are interpreted by a discriminating radiologist, *it is not only safe but specific in the highest degree.*

David Littmann, M.D.
Veterans Administration Hospital
1400 Veterans of Foreign Wars Parkway
West Roxbury, Mass. 02132

Exaggerated natriuresis during salt loading in hypertensive states

The rejection of sodium by the kidney in hypertensive man during sodium loading has been the subject of extensive study by renal physiologists.[1]

In patients with arterial hypertension the natriuretic response to infusion of sodium is far greater than in normotensive individuals. In contrast, during low intake of salt there is no significant difference between the two groups in the amount of sodium excreted. This peculiar behavior of hypertensive patients to salt loading cannot be attributed to differences in preinfusion rates of excretion of sodium or to a greater increase in the concentration of serum sodium.[2] It has been suggested that this exaggerated natriuresis could be the result of the elevated renal arterial pressure per se. It has also been reported recently that elevation of systemic blood pressure in normotensive subjects after the administration of metaraminol is accompanied by an enhanced natriuretic response to rapidly infused salt.[3] However, no satisfactory explanation has yet been given.

The *recent work of Dr. Vondonkas* during the past 3 years dealing with the measurement of the concentration of sodium in renal tissue under control conditions and after the administration of various vasopressor agents has shed some *light on* a possible explanation of this salt losing phenomenon. Normally, because of the countercurrent concentrating and diffusion exchange mechanisms operating in the renal medulla, an increasing concentration of sodium is seen from the cortex to the tip of the inner medulla (papilla).[4] Under the influence of various vasopressors (phenylephrine, methoxamine) a further increase in the concentration of sodium in the medulla is observed.[5,6] In view of this experimental work, it is postulated that during a hypertensive state, because of the augmentation of the concentration of sodium in renal medullary tissue, the renal medulla becomes somewhat oversaturated with sodium and therefore no more solute can be reabsorbed after an acute intravenous salt loading. It is conceivable that a similar change in the concentration of sodium in the medulla may occur in the hypertensive patient in comparison with the normotensive subject. Thus it is suggested that the salt losing mechanism in hypertensive states is due principally to an increased concentration of sodium in the medulla. Furthermore, in view of the inverse relationship between the concentration of sodium and the blood

flow in the medulla.[14] It is postulated that the events leading to the accumulation of sodium in this area are secondary to a diminished renal medullary blood flow. More studies are in progress in our laboratories for further elucidation of this fascinating aspect of renal physiology.

Ignatius J. Voudoukis, M.D.
John R. Caldwell, M.D.
Division of Hypertension
Henry Ford Hospital
2799 West Grand Blvd.
Detroit, Mich. 48202

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A critique of the cardiac index and the introduction of a more rational index of cardiac performance

Currently, cardiac output is related to surface area in order to establish a measure of "normality," the cardiac index. The use of this cardiac index has been severely criticized by Tanner.[1] I shall not discuss Tanner's arguments here but merely present the case for another index which has the advantage of being a more rational and direct measure of cardiac performance. This index has already been proposed several times.* I shall attempt to show that cardiac output should be related to metabolism rather than surface area, body weight, or lean body mass. The current cardiac index suffers from the fact that it is unrelated to the *functional meaning* of cardiac output. I shall attempt to clarify this statement.

Basal metabolism has a *direct* functional link with lean body mass: the greater the number of active cells, the higher the total (basal) metabolism. Hence it is logical to relate basal metabolism to lean body mass or its more accessible aspect, body surface area or body weight. However, the link between cardiac output and lean body mass is a far more tenuous one. Whereas the addition of each active cell contributes to an increase in basal metabolism by simply being there, such an addition does not in itself contribute to an increase in cardiac output. The only *reason for the cardiac output to* be as high as it actually is (under conditions of both

*It has been suggested by Reeve and ... on the basis of the ... argument ... They also refer to similar suggestions made ... 40 years ago.

rest and exercise) is to maintain an adequate transport of oxygen (and carbon dioxide) for the metabolic requirements. Whereas basal metabolism is directly linked to *lean body mass* (or surface area), cardiac output is *directly* linked, through homeostatic mechanisms, to metabolism or, better, to oxygen need. Hence, and this cannot be emphasized too strongly, if a rational choice is to be made between expressing cardiac output in terms of surface area (lean body mass) or in terms of metabolism, the latter should be selected.

It would at first sight appear that such a choice is immaterial since, with basal metabolism being related to lean body weight, the results reduce to essentially the same answer. We shall presently see that this is not so.

This selection leads to an alternative index of disarming simplicity. To avoid confusion we shall introduce the term *circulatory index* to designate this new cardiac index. This term is highly appropriate since the magnitude of cardiac output is the resultant of the interplay of all circulatory factors and not merely of the heart itself.

If we introduce a cardiac index defined by

$$\text{circulatory index} = \frac{\text{cardiac output}}{\text{oxygen consumption}} \quad (1)$$

the oxygen consumption is an even sharper measure than metabolism per se (note that we do not restrict this definition of cardiac index to *basal* metabolism), then, since by the Fick formula

$$\text{cardiac output} = \frac{\text{oxygen consumption}}{\text{(a-v) oxygen difference}} \quad (2)$$

that

$$\text{circulatory index} = \frac{1}{\text{(a-v) oxygen difference}} \quad (3)$$

Formula (3) shows that to obtain the new index of circulatory performance there is no need to measure cardiac output itself or metabolism. It suffices to measure the arteriovenous oxygen difference.

The advantage of this new index will be demonstrated by an example. We shall construct on the basis of standard tables a hypothetical man. Consider a man 1.75 meters in height and weighing 75 kilograms. From the DuBois nomogram the surface area is 1.9 M². Taking his basal heat production (after DuBois) to be 40 Cal. per hour per square meter of body surface, his basal metabolism *is found* to be 1.9 × 40 = 76 Cal. per hour. Let his nonprotein respiratory quotient be, say, 0.80. At this value the caloric value of 1 liter of oxygen is 4.8 Cal. Hence the oxygen consumption is 76 ÷ 4.8 = 16 liters per hour or 266 ml. per minute. An average normal value of the oxygen arteriovenous difference in the basal state is 4.5 volumes per cent (see, for example, *Handbook of Respiration*[4]). Hence his basal cardiac output is 266 ÷ 45 = 5.91 liters per minute. His classic cardiac index is 3.1, a normal value. The new index gives the (obviously) normal value of 22.2 ml. of blood per milliliter of oxygen.

Let us next assume that this person develops extreme hypothyroidism and halves his metabolism. Let us further assume that his cardiovascular system remains in excellent functional condition. His oxygen consumption will now be 133 ml. per minute. Since, by assumption, his cardiovascular system adapts perfectly, his oxygen a-v difference will remain at 4.5 volumes per cent. Hence his cardiac output will now be 2.96 liters per minute. The classic cardiac index will now be found to be 1.55, suggesting that his cardiovascular system is in very poor shape. This implication is inherent in the current cardiac index, for if the cardiac index is a measure of (the normality or abnormality of) cardiac function, then, if his cardiac index is grossly abnormal, the conclusion that his cardiac function is grossly abnormal is inescapable.

But we have postulated that his cardiovascular system is functionally normal, as is evidenced by the normal value of his arteriovenous oxygen difference of 4.5 volumes per cent. The proposed circulatory index does indicate the true state of affairs in this case of hypothyroidism. Using Formula (1) we obtain for the circulatory index 2,960 ÷ 133 = 22.2 ml. of blood per milliliter of oxygen, the same normal value as before the hypothyroid state (see above). On the basis of the new index we thus conclude that despite his extreme hypothyroidism his cardiac function is perfectly normal, in agreement *with the assumption. This example shows in a* striking manner to what kind of endless confusion the unfortunate use of the classic index may give rise.

Now it might be objected that the classic cardiac index *does* give a correct picture, since after all a cardiac output as low as 2.96 liters per minute is definitely abnormal for a man of his size under basal conditions. This may be so, but this interpretation (the only possible one) of the so-called cardiac index demonstrates that this is not a *cardiac* index but a *metabolic* index. The cardiac output is abnormally low, not because the circulation itself is deficient, but because basal metabolism is grossly deficient. It may be safely assumed that the cardiac index has been proposed on the basis of the following consideration. In the basal state, cardiac output is related to basal metabolism, and since basal metabolism is related to surface area, it follows that cardiac output is related to surface area.

For subjects with a normal basal metabolism and measurements in the basal state the current cardiac index appears to be applicable despite Tanner's criticism. The proposed circulatory index does not represent a basic departure from the current concept, *but forms a natural generalization of it. The* proposed circulatory index indicates the true cardiac condition not only under any value of basal metabolism, but with the added advantage that it is not restricted to the basal state, as is easily seen.

For the implementation of this new index it is obvious that one may proceed in two ways: (a) measure cardiac output and metabolism and use Formula (1) or (b) measure the oxygen a-v difference and use Formula (3). The latter procedure is only possible with the use of heart catheterization. It has the distinct advantage of obviating the need for measuring oxygen consumption (a bottleneck in many hospitals) during heart catheterization. It may

be objected that the body metabolism per se is also of interest but obviously this falls outside the domain of heart catheterization studies. If one wishes to avoid heart catheterization, cardiac output currently measured by using a tracer dilution method. The necessity of having to measure oxygen consumption separately to arrive at a rational index of cardiac performance is an inevitable complication with the use of any non-Fick method.

On the other hand, almost no extra time and trouble are involved in measuring oxygen consumption by any of the so called indirect Fick method such as the recently described simple rebreathing method.

However, whether a practical method exists for the convenient implementation of the proposed circulatory index, it seems clear that the current cardiac index should be abandoned in favor of some more rational index.

In view of the oft-observed longevity of traditional concepts, even when proved wrong, it would perhaps be useful if an authoritative committee would study this problem and publish its recommendation.

J. G. Defares, M.D.
Division of Theoretical Physiology
Department of Physiology, University of Leiden
Leiden, Netherlands

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Butazolidin angiitis and periangiitis simulating Aschoff nodule

L. K. (A 48-63), an elderly woman who had sustained a fracture of the femur, was admitted to this hospital, St. Francis General Hospital, Pittsburgh, Pennsylvania. Prior to operation it was observed that she had a skin eruption. This was attributed to Butazolidin, which was then discontinued. She died abruptly and a pulmonary embolus was thought to be the immediate cause of death.

However, the heart revealed extensive perivascular lesions characterized by a granuloma-like appearance. The purpose of this brief annotation is to call attention to the fact that some of the perivascular lesions simulate *Aschoff nodules* (see photomicrograph, Fig. 1). High power observation of the myocardial perivascular lesions reveal collections of cells resembling Anitschkow myocytes; there are also eosinophils, lymphocytes, and plasma cells.

The characteristic fibrinoid necrosis and multinucleated cells described in the Aschoff nodule are lacking in the lesion under discussion.

J. M. Edelstein, M.D.
Associate Director of Laboratory
St. Francis General Hospital and Rehabilitation Institute
45th Street and Penn Ave.
Pittsburgh, Pa. 15201

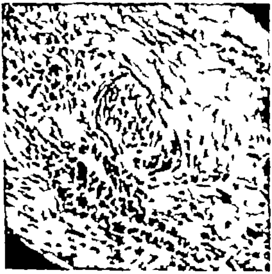


Fig. 1. Myocardium with vascular and perivascular lesion simulating Aschoff nodule. Hematoxylin and eosin. X450.

Letter to the Editor

The Mount Sinai Hospital
100th St and Fifth Ave
New York N Y 10029
December 15 1964

To the Editor

In reference to the article Prolonged Shock after Myocardial Infarction Relieved by ACTH and Cortisone in the issue of November 1964 one may question (1) the initial indication for vasopressor therapy (2) the efficacy of ACTH and cortisone in the clinical setting described and (3) the interpretation of the electrocardiograms

1 The patient was admitted to the hospital for severe chest pain with a blood pressure of 94/70 mm Hg pulse rate 65 and regular and the examination otherwise not remarkable The following morning after Demerol and several oral doses of Compazine the blood pressure fell to 72/60 a common occurrence after the use of these hypotensive agents But there was no other clinical evidence of shock and the pulse remained slow and regular Nevertheless the patient was started on pressor amines to elevate the blood pressure In view of the use of hypotensive medication and the absence of clinical signs of shock it appears likely that the blood pressure would have risen spontaneously as the effect of the Demerol and Compazine subsided This would have avoided subsequent difficulties with weaning from the pressor amines

The vasopressor drugs were then continued for 20 days because they were needed to maintain his systolic blood pressure above 100 mm Hg It is probable that in the clinical setting described the patient's usual blood pressure would have been only 94/70 mm Hg as on admission when there were no apparent physical abnormalities Obviously discontinuation of the pressor agents would necessitate a fall below 100 mm Hg Furthermore with prolonged use of the vasopressor drugs subsequent discontinuation causes an abnormal fall in blood pressure presumably until the body's own sympathomimetic agents are restored or function again Brief patience after such a fall in blood pressure is often rewarded by a gradual spontaneous rise The manifestations of the so-called shock (diaphoresis rapid thready pulse etc) that were noted when the drugs were discontinued were probably due to the vasopressor drugs themselves

2 In view of the foregoing the role of ACTH and cortisone is unconvincing since in similar circumstances in which it was stated that the vasopressor drugs could not be discontinued they were boldly removed despite transient hypotension with rapid spontaneous restoration of blood pressure and disappearance of the so-called shock symptoms without the use of ACTH and cortisone

3 The electrocardiogram of Sept 1 1961 reveals an S_1Q pattern incomplete right bundle branch block and an electrical axis of zero degrees The electrocardiogram of Oct 21 1961 is virtually unchanged except for the appearance of q waves in V_{1-4} which are too insignificant to support a diagnosis of myocardial infarction The electrocardiogram of May 1963 shows an axis of −30 degrees and normal electrical conduction The findings of a changing electrical axis and transient incomplete right bundle branch block may indicate acute cor pulmonale and suggest an alternative diagnosis of pulmonary embolism especially when there is no electrocardiographic or other laboratory evidence of acute transmural myocardial infarction

Regardless of the correctness of the clinical and electrocardiographic diagnoses there is much support for the contention that there was no need for the vasopressor drugs in the first place that subsequent problems were actually caused by the vasopressor drugs themselves and that there was no reason to require ACTH and cortisone subsequently

Herschel J Sharoff M D

Book reviews

RESPIRATORY FUNCTION IN DISEASE. By David V. Bates, M.D., Associate Professor of Medicine, McGill University, Montreal, Canada, and Ronald V. Christie, M.D., M.Sc., D.Sc., Sc.D., F.A.C.P., F.R.C.P., Professor and Chairman, Department of Medicine, McGill University, Montreal, Canada. Philadelphia, 1964, W. B. Saunders Co. 566 pages. Price $15.50.

This very good book of 23 chapters is concerned with the approach to the study of the patient, method, the normal lung and pulmonary diseases. Among the diseases discussed are asthma, emphysema, cysts and bullae, chronic bronchitis, pulmonary hypertension, bronchiectasis, fibrosis and others.

The book is well written, well illustrated with many good photographs of roentgenograms and documented with over 230 references. It is a good book for physicians and medical students not only because of the logical bedside approach to the problem, but also because the authors have adequately supported the clinical features of the diseases by modest and practical pulmonary function tests. The authors emphasize the important clinical findings without unnecessarily window dressing the data with pulmonary function tests which are so often uncritically and needlessly employed.

The book is highly recommended.

EXPERIENCE IN RENAL TRANSPLANTATION. By Thomas E. Starzl, Ph.D., M.D., Professor of Surgery, University of Colorado School of Medicine, Denver, Colo. Philadelphia, 1964, W. B. Saunders Co. 383 pages. Price $17.

This book, by one who has had much experience in transplanting kidneys in man, is certainly of interest to all concerned with organ transplantation. The author discusses the problems involved in renal transplantation and describes his own experiences. The technical surgical aspect of renal transplants is a minor one, and that is evident from this book and the literature. The major problem is primarily an immunological one and although evident in the book, the importance of the immunological difficulties is not emphasized sufficiently. The reactions and problems associated with the immuno-depressant agents are not well indicated. In fact, on page 3?7 the following Epilogue is found:

I[n] preparing this book, all statistics were brought up to date to June 1, 1964. As of September 1, 1964, there have been no additional deaths in the first 55 patients. Thus, the statistics in Chapters 1 to 17 and Chapter 20 are valid as they stand. All 34 surviving patients within the first group of 55 now be[i]ng ?? months or longer past operation. With th[e] ?th group there are now 13 patients who are [?] more than one year after transplantation.

I[n] the later patients, three additional deaths occurred (LD 56, LD 6?, and LD 64). These deaths influence the statistics only in Chapter 18, the chapter concerned with an evaluation of steroid pretreatment. These additional deaths have eliminated the advantage that the steroid pretreated patients seemed to have enjoyed during the early postoperative course; the number of deaths was just as large but did tend to occur at a later time. The three additional deaths occurred 151 (LD 56), 111 (LD 6?), and 65 (LD 64) days after operation.

Thus, the reader is made to believe that renal transplantation is quite a successful procedure. Nevertheless, this book should interest those working with organ transplantation and especially those who are interested in Dr. Starzl's opinions and experiences.

Among the subjects discussed are procurement and organization of data, selection of candidates for homotransplantation, preparation of recipient for transplantation, selection and evaluation of donors, antirejection therapy, causes of failure, complications, heterotransplantation, and pathologic changes in transplanted kidneys.

HANDBUCH DER MEDIZINISCHEN RADIOLOGIE. Bd. X, Teil 3 (Encyclopedia of Medical Radiology, Volume X, Part 3: Roentgen Diagnosis of the Heart and Blood Vessels). Edited by H. Vieten. Berlin, 1964, Springer Verlag. ?53 pages.

This is an excellent addition to the series of the Encyclopedia. It is well written and profusely illustrated with excellent radiographs. Unfortunately, all chapters are not in English for the English-speaking physicians, but it is hoped that the entire series will be translated into English.

The book includes chapters on radiography of the pulmonary vascular system, abdominal aorta and its branches, the portal system, the inferior vena cava, arteries of the extremities, peripheral veins, cerebral arteries, and the carotid arteries. The angiograms are excellent. The presentations are discussed not only from a strictly clinical point of view, but also from the anatomic and physiologic aspects.

The book is highly recommended.

L'ELETTROCARDIOGRAMMA NELLE CARDIOPATIE CONGENITE. By N. Perna and V. Jacono. Rome, 1964, Societa Editrice Universo. ?6? pages. Price 6,000 lire.

This book on the electrocardiogram in congenital heart disease is a fairly good one. The common defects are discussed, but unfortunately very few tracings are shown. Each chapter is supported by a good bibliography. This should be a useful book, especially since there are so few [on] the subject.

ÜBER DEN WERT RETINALER GEFÄSSVERÄNDERUNGEN IN DER DIAGNOSTIK DER ARTERIOSKLEROSE. By Otto Erich Lund. Basel, 1964. S. Karger. 153 pages, 56 figures, 45 tables. Price $11.50.

This is a useful book that helps to overcome the difficulties in the proper interpretation of ophthalmological findings in relation to atherosclerosis. The basis for the original observations was a histologic correlation of findings of atherosclerotic changes in the eye and other organs; thus the fact of a close correlation of retinal sclerotic changes with similar changes in other organs such as the brain was confirmed. This was particularly true when there were atherosclerotic changes in other typical locations. Moreover, the ophthalmologic and histologic findings in the eye seem to be in good agreement, which no doubt is a fact that supports the value of positive findings in the clinical evaluation.

AUTOREGULATION OF BLOOD FLOW. (Proceedings of an International Symposium held June 10-12, 1963, in Indianapolis, Ind.) Edited by Paul C. Johnson, Ph.D. New York, 1964. The American Heart Association, Inc. 291 pages. Price $3.

This symposium on autoregulation of blood flow is a timely and important one. Some of the more important concepts of interest to students, clinicians, and physiologists are reviewed. Among the subjects discussed are regulation of blood flow to muscle and skin, reactive hyperemia and metabolic factors in autoregulation, autoregulation of blood flow in the myocardium, and autoregulation of renal and cerebral blood flow. This compendium consists of a series of papers presented in Indianapolis in June, 1963. The monograph should be very useful.

VASCULAR ROENTGENOLOGY. By Robert A. Schobinger, M.D., Department of Surgery, Clinic St. Anna, Lucerne, Switzerland, and Frank F. Ruzicka, Jr., M.D., Department of Radiology, St. Vincent Hospital and Medical Center, New York, N. Y. New York, 1964. The Macmillan Co. 747 pages. Price $32.

The vascular roentgenography discussed includes not only arteriography and phlebography but lymphography as well. These fields are developing rapidly, and this very practical book is highly recommended.

CARDIOPULMONARY HEMODYNAMICS IN HEALTH AND DISEASE. By Carsten Muller, M.D., Ph.D., Associate Professor of Medicine, Lecturer in Cardiology, University of Oslo, Oslo, Norway. Springfield, Ill., 1964. Charles C Thomas, Publisher. 196 pages. Price $7.50.

This is a brief discussion of hemodynamic phenomena in the lungs of normal people and in patients with pulmonary disease. The author summarizes the anatomy and physiology of the pulmonary circulation. He indicates the action of selected vasoactive drugs on the pulmonary circulation and the influence of the nervous system on the regulation of pulmonary circulation. The normal hemodynamics are briefly presented and the important reports in the literature are summarized. Cardiac failure and the pulmonary circulation in chronic pulmonary diseases are reviewed. The section on the mechanisms and disturbances in congestive heart failure (Chapter V) is diffuse and not critical. The reader will find these discussions confusing. However, it is of interest to see how an author interprets and summarizes the conflicting and complex literature and experiments in his own mind and in a report for others. Unfortunately, the author merely reports findings without being critical of them.

There is a fairly good although selected bibliography at the end of the book.

This book should be of interest but must be read with caution and full awareness that most of the physiologic and clinical aspects of cardiopulmonary hemodynamics are still unsettled and poorly understood.

PULSATILE BLOOD FLOW. Edited by Ernst O. Attinger, M.D. New York, 1964. Blakiston Division, McGraw-Hill Book Co. 462 pages. Price $17.50.

This is the report of the proceedings of the First International Symposium on Pulsatile Blood Flow held in Philadelphia from April 11 through April 13, 1963. The book is a good one and should interest all who are engaged in the study of hemodynamic phenomena and the flow of blood in blood vessels. Not only are problems in rheology and the regulation of the circulation discussed, but interesting aspects of the pump, the heart, are also presented.

Announcement

AN INTERNATIONAL SYMPOSIUM ON THE CARDIOVASCULAR AND RESPIRATORY EFFECTS OF HYPOXIA, sponsored by the Ontario Heart Foundation, will be held on June 3, 4, and 5, 1965, at Queen's University, Kingston, Ontario, Canada.

Registration is limited. Direct inquiries to Dr. J. D. Hatcher, Department of Physiology, Queen's University, Kingston, Ontario, Canada.

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Editorial

Diabetes insipidus

*Elbert P. Tuttle, Jr., M.D.**
Atlanta, Ga.

Diabetes insipidus is lack of the antidiuretic hormone vasopressin, and renal diabetes insipidus is lack of renal response to vasopressin in the absence of other diagnosable kidney disease. Despite the magnificent characterization and synthesis of vasopressin by du Vigneaud and his colleagues, a satisfactory means of measuring blood levels of circulating hormone is not available. Even less specific bioassays have proved to be so difficult as as to preclude general use. In consequence, the diagnosis of diabetes insipidus rests on physiologic tests. The complexity of the controls of water balance is such that errors in diagnosis, both false positives and false negatives, occur, and evaluation of the degrees of vasopressin deficiency is virtually impossible. Errors may be minimized by a thorough understanding of the physiology of water balance.

The etymological connotations of the term *diabetes insipidus* provide a definition of the clinical problem as it usually presents. Flavorless urine in excess is an inconvenience to the patient and a challenge to his physician. It demands relief as an annoying symptom; it may be a sign of focal disease; and as an experiment of nature it casts light on the mechanisms of control of water balance. It must be recognized, however, that not all patients with a large flow of dilute urine lack the benefits of vasopressin, nor do all patients deficient in vasopressin produce large volumes of dilute urine.

Patients with vasopressin deficiency fall into two major functional categories: those with polyuria-polydipsia and those without. Fig. 1 indicates the differential diagnosis of excessive water turnover. At the first level, primary polydipsia must be differentiated from primary polyuria. Primary polydipsia leads to a slightly expanded total body water and, if extreme, to dilutional hyponatremia and hypotonicity. Primary polyuria leads to a deficit of total body water and occasionally to hypernatremic and hypertonic dehydration.

These may be readily distinguished by the simple restriction of the intake of fluid to 1 liter a day on a diet that provides 600 mOsm. of solute for excretion. A diet containing 60 Gm. of protein and 6 Gm. of NaCl a day approximates this. In both types of patients some loss of

From the Department of Medicine, Georgia Heart Association Chair of Cardiovascular Research, Emory University School of Medicine, Atlanta, Ga.

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*Address: Department of Internal Medicine, Emory University School of Medicine, 69 Butler St., S.E., Atlanta, Ga. 30303.

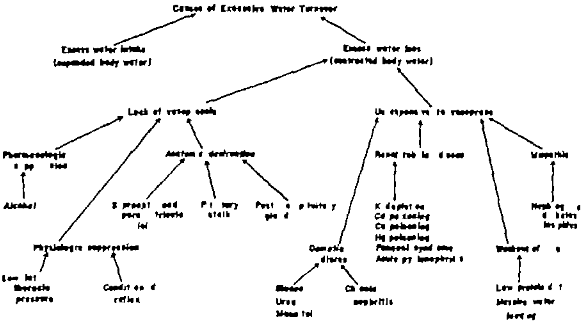


Fig. 1. Differential diagnosis of excessive water turnover.

weight may occur, but the patient with polydipsia will concentrate his urine above 600 mOsm./Kg. H_2O, reduce its volume, stabilize his body weight, and maintain normal body composition with serum sodium at less than 145 mEq./L. and serum osmolality below 290 mOsm./Kg. H_2O. The patient with primary polyuria will continue in negative water balance with a urine containing 50 to 450 mOsm./L. (specific gravity 1.001-1.015). He will give evidence of dehydration with loss of total body and intravascular water to the point of a rising pulse rate, falling blood pressure, and, if severe, falling glomerular filtration rate. His serum osmolality will rise above 300 mOsm./Kg. H_2O.

The symptom of thirst may well fail to reflect body fluid balance, since psychogenic polydipsia may have thirst as its main characteristic, and since some brain stem lesions impairing vasopressin secretion also damage the thirst center. In other types of primary polyuria, parallel loss of sodium may minimize thirst. In most instances, however, the patient with vasopressin deficiency will suffer from intense thirst.

It has occasionally been observed[1] that in patients with marked and prolonged polydipsia, maximum urinary concentration may be limited and that even with a restriction of the intake of water dilute urine may intermittently continue to be excreted. In spite of this, the capacity to conserve water is adequate to protect against dehydration. This defect of concentration has been attributed to the washout of urea or sodium from the renal medulla with large flows of urine, but with moderate dehydration over several days this defect is corrected.[1] The risks of dehydration are negligible if care is taken to monitor the pulse rate and blood pressure and serum osmolality (keep ≲ 300 mOsm./Kg. H_2O) or serum sodium concentration (keep ≲ 150 mEq./L.). Dehydration to a fixed percentage of body weight loss is not an adequate test, because some patients with polydipsia do have on board an indeterminate amount of extra water. Physiologic evidence of dehydration is the end point of this test.

If an excessive turnover of water is found to be due to primary polyuria, the next point to be ascertained is whether this is attributable to vasopressin deficiency or to inability of the kidney to respond to the antidiuretic hormone. The response to exogenous vasopressin provides the answer. Under conditions of mild dehydration as described above, on a 600 mOsm. normal

diet and 1 liter of water a day in a steady cardiovascular state, exogenous aqueous vasopressin 200 mU in 500 ml of normal saline intravenously in 1 hour, or 5 units of vasopressin tannate in oil* intramuscularly 8 to 12 hours before testing will cause a rise in urinary osmolality to > 600 mOsm / kg H_2O with a corresponding fall in the flow of urine by a similar reciprocal fraction if the polyuria is due to insufficient circulating vasopressin, i.e., if the patient has diabetes insipidus. Failure to respond with a rising concentration of solute in a falling volume of urine indicates a kidney which cannot respond to antidiuretic hormone. If the administration of vasopressin causes only a mild increase in urine concentration above that achieved with dehydration, this implies both vasopressin deficiency and vasopressin resistance.

If a lack of endogenous vasopressin is proved by responsiveness to the administered hormone in the dehydrated polyuric patient, this may be attributable to the destruction of the sites of its synthesis, transport, or storage in the brain and pituitary, or to pharmacologic or physiologic suppression of its release. Lesions in the supraoptic or paraventricular nuclei, in the pituitary stalk, or in the posterior pituitary gland are major causes of true diabetes insipidus. Tumors, both malignant and benign, including eosinophilic granulomas, craniopharyngiomas, anterior pituitary tumors of various sorts, metastatic tumors, and suprasellar cysts *may interfere* with the synthesis or release of vasopressin. The Hickey-Hare[3] test of rapid infusion of hypertonic saline provides an acute stimulus less strenuous than dehydration to demonstrate failure to concentrate the urine in the face of hyperosmolality of the serum in diabetes *insipidus*. It adds nothing to the diagnosis already proved by dehydration to serum osmolality of 300 mOsm / kg H_2O. Other tests, such as the injection or inhalation of nicotine or morphine to release antidiuretic hormone, give little additional information on the site of the lesion. Radiographic studies of the sella to demonstrate enlargement, erosion of the clinoids, and calcification are most useful in localization of lesions producing diabetes insipidus.

The only pharmacologic agent presently thought to inhibit the release of antidiuretic hormone is alcohol. The usual conditions of its ingestion are such that polydipsia and polyuria conspire to produce a large turnover of fluid, and in most cases the etiological agent is clearly in evidence. For this reason it is of only passing interest in the present context. Physiologic suppression of secretion of the antidiuretic hormone may be induced by negative pressure breathing[4] or inhalation against resistance, which reduces mean intrathoracic pressure and stretches low pressure vascular compartments in the chest. Other physiologic causes of polyuria, such as a reduction in sympathetic tone to the kidneys or an increase in renal perfusion pressure,[6] may occasionally cause negative water balance or obscure the response to vasopressin. Psychological depression of the release of vasopressin was suggested in one compulsive water drinker reported by DeWardener.[7] The polyurias seen under circumstances such as these are usually transient, although they may be brisk.

If polyuria and hyposthenuria are unresponsive to exogenous vasopressin and dehydration, then a failure of the normal renal response to the hormone must be postulated. Under conditions of osmotic diuresis the kidneys are unable to reduce flow or to concentrate the urine in response to vasopressin. As shown by Wesson and Anslow,[5] a positive free water clearance may be observed. This cause of resistance to vasopressin occurs in diabetes mellitus and urea and mannitol diuresis. The finding of glycosuria, the development of high osmolar clearance, or the excretion of excessive solute per unit of time leads to the diagnosis of osmotic diuresis. Hyperglycemia after cerebral vascular accidents and high protein tube feeding in comatose patients have introduced osmotic diuresis into the differential diagnosis of polyuria when diabetes insipidus is suspected after brain injury.

Diseases of the kidney which destroy nephrons lead to vasopressin resistant isosthenuria with moderate polyuria in

* It is essential [illegible] warm and suspend the small b[illegible] of brown powder before [illegible] jecting [illegible] oil has no [illegible] property.

glomerulonephritis and pyelonephritis although with severe dehydration the urine may reach a specific gravity of 1.020. This may be another manifestation of osmotic diuresis in a reduced number of nephrons as postulated by Bricker.[9] In these cases polyuria is often mild. The impairment of renal response to vasopressin in diseases of the renal tubules, such as in potassium depletion, calcium or vitamin D poisoning, early pyelonephritis, or Fanconi syndromes, is not due to osmotic diuresis. The nature of this blockade of hormone action is obscure. Disturbance of tubular transport of sodium and water, disturbance of blood flow, and destruction of the countercurrent system have been postulated. All of these might be considered to be examples of renal diabetes insipidus. Each must be evaluated and by appropriate studies of history, physical examination, serum electrolytes, microbiology, and pathology of the kidney, a nosological diagnosis of the renal disease made.

Of particular interest has been the problem of nephrogenic diabetes insipidus. This inherited sex-linked entity appears as a specific failure of the kidney to respond to vasopressin in the absence of other evidence of kidney disease. It appears soon after birth in boys, may clear by the age 2 or may last to adulthood,[14] and women in families with the disease show some impairment of concentrating ability.[11] The classic picture is the irritable, febrile, retarded male infant with dehydration and a large turnover of water. A reduction in the intake of solutes reduces the flow of urine, as do some diuretics by a mechanism not understood at present.

The occurrence of an excessive turnover of water in many cases of diabetes insipidus is a readily discernible clue to the presence of an abnormality in the water control mechanism. What of the possibilities of vasopressin deficiency in the absence of marked polyuria? For years it was argued that ablation of the anterior pituitary "cured" diabetes insipidus. Indeed, it may cure the polyuria but it does not restore the secretion of vasopressin.

A number of conditions are necessary for a lack of vasopressin to cause polyuria. The volume of urine is dependent not only upon its solute concentration but also on the quantity of solute demanding excretion. A volume of 3 L. of urine a day to excrete 300 mOsm. of solute might not be considered to be excessive, but a volume of 9 L. to excrete 900 mOsm. would certainly seem so to the patient. Thus a drastic reduction in the total solute turnover which frequently occurs with destruction of the anterior pituitary may reduce polyuria as shown by Leaf and associates.[12] Starvation has a similar effect.

A second critical factor in the polyuria of diabetes insipidus is the condition of the renal circulation. Berliner and Davidson[13] showed that a reduction in renal perfusion pressure or flow could cause increased reabsorption of filtered water to a degree that raised the osmolality of the urine from 85 to 388 mOsm./Kg. H_2O in the water-loaded dog. A fourfold rise in the concentration would abolish most levels of polyuria. This is important in man with renal disease, vascular disease, and congestive heart failure. Any of these diseases may prevent the diuresis of vasopressin deficiency by reducing renal perfusion pressure or flow.

These considerations make clear some of the reasons that physiologic tests using the flow and solute concentration of the urine as the index of hormonal secretion are such imprecise tools. The expected osmolality of the urine and its rate of flow or the osmolal and free water clearances vary markedly depending upon such factors as dietary protein, intake of sodium and potassium, circulatory competence and level of sympathetic-parasympathetic tone, and pituitary, adrenocortical, renal, and liver function.

Until these variables are specified or controlled it is difficult to set up precise physiologic function tests to estimate the level of secretion or action of vasopressin. It is for this reason that no simple diagnostic criterion for the diagnosis of vasopressin deficiency can be made. Each patient with the complaint of either polyuria or intracranial disease likely to involve the anterior hypothalamus and pituitary should be evaluated for the presence and nature of disturbance of water balance. Until assay of blood vasopressin is available, tests of urine osmolality and volume must be read with broad

understanding of the nonhormonal factors influencing renal concentrating ability

Treatment must be tailored to the cause of the polyuria In diabetes insipidus both central and renal regulation of the solute content of the diet can make a threefold difference in urine volume Adequacy of the thirst center to preserve water balance must be carefully evaluated Replacement therapy when required is readily achieved by linguets snuff nasal pledgets and repository injection

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Clinical communications

The direct brachial arterial pulse-pressure curve in the evaluation of patients with aortic valvular stenosis

Abner J. Delman, M.D.
*Garet M. Gordon, M.D.***
*Robert Eisenberg, M.D.***
*Doris J. W. Escher, M.D.****
*Robert Rosenblum, M.D.*****
New York, N. Y.

The relationship of the central and peripheral pulse pressure curves in normal man, in patients with aortic stenosis, and in experimentally produced aortic stenosis has been discussed in the literature.[1] However, there has not been a consistent opinion concerning the diagnostic value of the brachial arterial pulse pressure curves in patients with aortic stenosis,[4-7] despite the fact that in this condition, in contradistinction to the normal state, the direct brachial arterial pressure curve resembles the central arterial pulse contours.[8-11] Since the techniques of left heart catheterization for quantitatively evaluating the gradient across the aortic valve are not without complications,[12-14] it was thought that an attempt should be made to determine the value of these brachial arterial tracings as a screening test for the presence of aortic stenosis.

Material and methods

The brachial arterial pulse pressure curves of 80 patients (age range of 2 to 64 years) were recorded and analyzed. These were divided into five groups on the bases of underlying cardiac states as follows:

1. *Severe aortic valvular stenosis (24 patients—18 acquired and 6 congenital).* Those patients with a normal cardiac index (C. I.) with a peak to peak or mean systolic gradient of over 50 mm. Hg, or with a decreased cardiac index with a valve area calculated by the method of Gorlin and Gorlin[15] to be less than 0.75 cm.[2]

2. *Mild aortic valvular stenosis (16 patients—9 acquired and 7 congenital).* Those patients with gradients less than 50 mm. Hg across the valve with a normal cardiac index, or with a decreased cardiac

From the Cardiac Catheterization Laboratory and the Cardiology Service, Medical Division, Montefiore Hospital, New York, N. Y.

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*Adjunct Attending Physician, Cardiology Service, Medical Division, Montefiore Hospital. Address: Montefiore Hospital, 210th St. and Bainbridge Ave., New York, N. Y. 10467.

**New York Heart Association Trainee 1961-1962. Formerly Assistant Attending Physician, Medical Division, Montefiore Hospital.

***Associate Attending Physician, Pediatric Division, and Research Associate in Pediatric Cardiology, Cardiology Service, Montefiore Hospital; Assistant Professor of Clinical Pediatrics, Albert Einstein College of Medicine.

****Associate Attending Physician, Cardiology Service, Medical Division, and Physician-in-Charge, Cardiac Catheterization Laboratory, Montefiore Hospital; Lecturer in Medicine, Columbia University.

*****Adjunct Attending Physician, Cardiology Service, Medical Division, and Research Associate, Montefiore Hospital; Teaching Assistant, New York University School of Medicine.

index and a valve area calculated to be greater than 0 75 cm

This criterion for valve area in both mild and severe stenosis related only to patients over 16 years of age

3 *Mitral stenosis—normal C I* (7 patients) Those patients with a cardiac index in the range of 2 8 to 3 6 L /min /M² and no evidence of aortic stenosis

4 *Mitral stenosis—low C I* (11 patients) Those patients with a cardiac index of less than 2 8 L /min /M² with no evidence of aortic stenosis

5 *No heart disease* (22 patients) Hospitalized patients without clinical evidence of heart disease who were comparable in age to the patients in Groups 1 4

Patients with aortic stenosis with significant mitral insufficiency were not included in the study because mitral insufficiency itself will shorten the systolic ejection time [14,21] Patients with aortic stenosis and hemodynamically significant aortic insufficiency were also excluded Significant aortic and mitral insufficiency were determined by accepted clinical hemodynamic and angiocardiographic criteria

All of the patients in Groups 1 4 and 8 of the patients in Group 5 had concurrently performed right and left heart catheterizations Gradients across the mitral valve were obtained by the analysis of simultaneous pulmonary artery wedge or direct left atrial and left ventricular pressures The direct left atrial measurements were obtained by the transseptal technique [22] The left ventricular pressure was obtained either by the retrograde Seldinger method [3] using a femoral artery or by direct percutaneous left ventricular puncture [23] Mean and peak to peak systolic gradients across the aortic valve were obtained from the simultaneous left ventricular and brachial arterial pressures Cardiac output was measured by the direct Fick principle with analyses of the respiratory gases by the method of Scholander [4] and the blood gases by the method of Van Slyke and Neill The brachial arterial pulse pressure tracings were recorded with a Cournand needle placed in the right or left brachial artery All measurements of pressure were recorded on the Electronics for Medicine multichannel recorder using Statham gauge transducers

The following information was obtained from the brachial arterial tracings (1) the time in seconds from the initial rise to the maximum systolic pressure (upstroke time) (2) the rate of rise in the initial slope of the brachial curves in millimeters of mercury per second (the upstroke velocity) and (3) the time in seconds from the initial rise in the brachial arterial pressure curve to the dicrotic notch (systolic ejection time)

Results

The data from each group of patients is tabulated in Tables I and II

Brachial arterial upstroke time (*Fig 1*) In the 22 patients without heart disease the brachial arterial upstroke time varied from 0 06 to 0 19 second with a mean of 0 11 second Only one patient had an upstroke time greater than 0 14 second In 23 of the 24 patients with severe aortic stenosis (4 with coexistent mitral stenosis) the upstroke time was equal to or greater than 0 18 second with a range of 0 18 to 0 30 second One patient with severe aortic stenosis and mitral stenosis had an upstroke time of less than 0 18 second The mean for the 24 patients was 0 22 second An upstroke time equal to or greater than 0 18 second was also noted in 8 of the 9 patients with mild acquired aortic stenosis with a range of 0 18 to 0 25 second One patient had an upstroke time of 0 11 second The mean for the 9 patients was 0 19 second Six of the 7 patients with mild congenital aortic stenosis had upstroke times of less than 0 18 second with a range of 0 10 to 0 12 second The seventh patient had an upstroke time of 0 20 second The mean for the 7 patients was 0 13 second In the 7 patients with isolated mitral stenosis and normal cardiac indices the upstroke time was 0 075 to 0 18 second with a mean of 0 12 second In the 11 patients with isolated mitral stenosis and reduced cardiac indices the upstroke time was 0 07 to 0 16 second with a mean of 0 11 second A reduced cardiac index did not prolong the upstroke time in any group of patients

Brachial upstroke velocity (*Fig 2*) The 22 patients without heart disease had a mean upstroke velocity of 999 mm Hg per second with a range of 595 to 1 710 mm Hg per second In the patients with

Table I

Patient	Sex Age (yr)	CO (L./min.)	CI (L./min./M²)	Mean gradient (mm. Hg)	Peak grad ent (mm. Hg)	LV pressure (mm. Hg)	BA pressure (mm. Hg)	Mitral gradient (mm. Hg)	Ejection time (sec.)	Cardiac cycle (sec.)	Upstroke time (sec.)	Upstroke velocity (mm. Hg/sec.)
Severe Aortic Stenosis—Acquired												
I M	M 62	4.05	2.33	40	40	136/18	96/66	0	0.3	0.48	0.25	400
R I	F 64	4.34	1.89	35	87	230/21	143/83	0	0.40	0.90	0.24	510
N M	M 51	2.60	1.39	56	73	150/32	77/57	0	0.29	0.82	0.21	457
M F	M 50	4.38	2.40	72	97	228/28	131/85	0	0.43	0.85	0.23	525
M S	M 50	5.13	2.80	56	58	182/9	120/66	8.2	0.34	0.72	0.18	512
L D	M 44			59	88	189/42	101/59	0	0.47	0.79	0.2	370
W N	M 55	2.60	1.63	40	65	155/4	90/44	101 D	0.36	1.10	0.24	310
L C	M 36	2.53	1.44	56	85	181/22	96/70	0	0.31	0.65	0.22	219
N C	M 51			8	83	225/16	142/85	0	0.34	0.64	0.21	500
I F	M 49			64	65	205/15	141/88	0	0.33	0.70	0.24	379
N F	M 37	2.68	1.5	32	36	136/18	100/64	8.2	0.38	0.95	0.20	480
J N	M 43	5.4	2.5	73	80	180/13	100/60	0	0.35	0.82	0.20	260
F N	M 34	5.95	4.2	62	65	197/17	127/62	0	0.38	1.00	0.30	387
S S	M 50	3.8	2.3	40	42	162/35	120/81	15	0.28	0.43	0.14	418
F B	M 54	5.4	3.8	58	70	190/15	120/60	0	0.47	0.85	0.30	375
F D	F 53				94	230/15	176/78	0	0.37	0.55	0.19	350
N L	M 55	4.9	2.6	54	50	180/12	130/64	0	0.32	0.90	0.20	387
I S	F 50	3.9	2.44	45	40	180/10	140/70	15	0.32	0.80	0.18	375
Severe Aortic Stenosis—Congenital												
R I	M 8				73	150/13	77/57	0	0.27	0.62	0.23	665
R S	M 2				170	180/4	60/48	0	0.29	0.48	0.19	375
J L	M 50				86	201/42	115/60	0	0.33	0.61	0.20	400
C C	M 15				135	230/16	95/72	0	0.33	0.90	0.26	390
L D	F 34				108(OR)		120/80	0	0.35	0.73	0.22	24
L W	M 10				150	240/13	91/61	0	0.30	0.50	0.20	300
Mild Aortic Stenosis—Acquired												
I M	F 54	4.25	2.29		10	170/15	160/80	0	0.38	0.93	0.21	650
N B	M 43	6.76	3.47	10	22	177/17	155/75	0	0.29	0.78	0.21	660
T D	M 30	4.01	2.31	15	25	165/15	140/80	0	0.38	0.76	0.20	665
C K	F 37				16	100/13	84/40	0	0.28	0.90	0.18	650
R N	M 37	4.40	2.93	[illegible]	32	134/10	102/58	10	0.37	0.71	0.20	610
C B	F 41	2.0	1.88	19	20	143/12	123/74	0	0.25	0.66	0.20	600
H D	M 49	5.52	2.82	41	40	164/10	1?4/73	0	0.30	0.75	0.20	750
J O	M 42	5.9	2.9	42	45	150/10	105/60	0	0.38	0.60	0.18	320
R D	F 57	5.50	2.78	30	35	130/8	95/50	10	0.32	0.70	0.11	500

Mild Aortic Stenosis—Congenital												
¶ C	F	13			17	117/7	100/68	0	0 30	0 73	0 10	650
R C	M	13			30	145/3	115/79	0	0 29	0 77	0 20	474
J M	M	34	5 5	2 6	10	118/5	108/81	0	0 30	0 80	0 17	675
L I	M	16			0	119/3	120/77	0	0 28	0 95	0 11	925
M I	M	13			10	115/14	105/50	0	0 33	0 80	0 12	625
M P	M	15			30	140/17	110/70	0	0 36	0 90	0 12	700
J T	M	15			25	160/20	135/88	0	0 32	0 60	0 12	500
Mitral Stenosis—Low Output												
E G	F	56	3 4	2 1		134/8	138/64	8 4	0 20	0 62	0 07	1 030
L A	F	49	2 8	1 8		98/8	104/59	16 0	0 22	0 83	0 14	575
R F	F	47	2 8	1 7		95/7	98/45	7 5	0 32	1 37	0 16	645
C C	M	44	3 72	1 85		124/0	130/82	15 0	0 29	0 89	0 15	400
I I ‡	F	52	3 66	2 44		116/8	118/69	12 0	0 28	0 70	0 11	950
A N	F	54	3 32	2 37		127/8	179/63	5 0E D	0 26	1 10	0 08	800
I L ‡	F	55	4 65	2 64		100/7	106/60	12 0	0 28	0 70	0 11	950
K Q ‡	F	45	3 25	2 13		101/4	106/58	6 0E D	0 31	1 00	0 15	800
J I ‡	F	21	3 92	2 65		100/3	105/60	4 0F D	0 30	0 94	0 10	443
J B	F	40	2 30	1 56		79/7	84/60	19 0	0 18	0 47	0 08	524
J A	F	42	2 72	1 71		105/6	108/65	14–15	0 24	0 66	0 08	719
Mitral Stenosis—Normal Output												
J D	F	34	5 24	2 96		134/5	138/69	6 6	0 28	0 86	0 18	640
S K	M	24	4 85	2 87		108/5	109/59	13 0	0 34	0 96	0 09	948
M D	M	31	7 73	3 71		95/5	100/60	10 0E D	0 29	0 76	0 11	453
J I	M	39	5 24	3 27		112/5	115/62	18 0	0 30	0 94	0 13	658
R I	F	22	5 16	3 22		145/10	150/85	23 0	0 18	0 45	0 10	850
E W	F	30	5 77	3 64		105/4	109/62	25 0	0 26	0 60	0 075	1 000
A S	F	47	4 90	3 14		100/10	104/56	5 5	0 31	0 96	0 15	740

*M ... (... efficiency ...) ... [illegible]
†C ... calculated by E.D (...) ... [illegible]
CO Cardiac output CI Cardiac index LV Left ventricular BA brachial arterial
‡P ... [illegible]

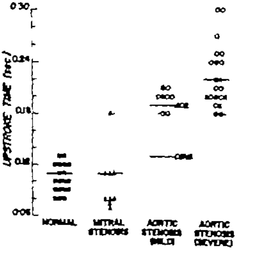


Fig. 1. Upstroke time in normal patients and in patients with mitral stenosis, mild aortic stenosis, and severe aortic stenosis. The lines through the columns represent means of each group. X, Congenital aortic stenosis. O, Acquired aortic stenosis. ●, Combined aortic and mitral stenosis.

severe aortic stenosis one patient with congenital stenosis had an upstroke velocity greater than 600 mm Hg per second. The range for the 24 patients in this group was 218 to 665 mm Hg per second with a mean of 437 mm Hg per second. Seven of the 9 patients with mild acquired aortic stenosis and 5 of the 7 with mild congenital aortic stenosis had upstroke velocities equal to or greater than 600 mm Hg per second. The range for the 16 patients with mild stenosis was 320 to 925 mm Hg per second with a mean of 602 mm Hg per second. The group with mitral stenosis and normal cardiac indices had a range of 453 to 1,000 mm Hg per second with a mean of 756 mm Hg per second. Only one of these 7 patients had an upstroke velocity of less than 600 mm Hg per second. However, 4 of 11 patients with mitral stenosis and decreased cardiac indices had upstroke velocities of less than 600 mm Hg per second. The range for all 11 was 400 to 1,030 mm Hg per second with a mean of 694 mm Hg per second.

Systolic ejection time (*Figs. 3 and 4*)

Table II. Data in random control subjects

Patient	Diagnosis	Sex	Age (yr.)	ECG	Blood pressure (mm. Hg)	Cardiac size (x-ray)	Cardiac cycle (sec.)	Ejection time (sec.)	Upstroke time (sec.)	Upstroke velocity (mm. Hg/sec.)
F. D.	Tuberculosis	M	50	Normal	135/80	Normal	0.53	0.23	0.12	900
S. S.	Tuberculosis	M	26	Normal	135/78	Normal	0.88	0.28	0.06	1,635
L. B.	Tuberculosis	F	24	Normal	110/70	Normal	0.73	0.28	0.09	770
L. B.	Tuberculosis	F	29	Normal	118/62	Normal	0.70	0.30	0.12	668
L. I.	Normal	M	16	Normal	134/84	Normal	1.10	0.27	0.10	943
A. M.	Multiple sclerosis	M	60	Normal	190/80	Normal	0.94	0.48	0.19	1,710
S. F.	Carcinoma of lung	M	37	Normal	135/72	Normal	0.68	0.30	0.12	787
N. B.	Carcinoma of breast	F	62	Normal	126/[illegible]4	Normal	0.74	0.27	0.13	780
L. C.	Carcinoma of lung	M	63	Normal	125/64	Normal	0.78	0.25	0.09	1,020
R. R.	Reticular cell sarcoma	M	27	Normal	140/90	Normal	0.45	0.28	0.13	597
A. M.	Carcinoma of stomach	M	50	Normal	130/68	Normal	0.53	0.22	0.11	1,170
M. O.	Carcinoma of stomach	M	73	Normal	162/76	Normal	0.67	0.25	0.11	1,240
M. R.	Carcinoma of lung	M	54	Normal	120/63	Normal	0.48	0.22	0.12	1,040
L. J.	Tuberculosis	M	28	Normal	160/88	Normal	0.56	0.21	0.10	1,003
F. C.	Normal	F	11	Normal	120/[illegible]0	Normal	0.90	0.26	0.10	1,100
P. K.	Normal	M	49	Normal	150/[illegible]0	Normal	0.70	0.22	0.08	900
M. M.	Normal	F	8½	Normal	140/80	Normal	0.60	0.23	0.07	1,000
L. P.	Normal	M	16	Normal	154/80	Normal	1.00	0.28	0.10	900
J. S.	Normal	M	8	Normal	138/[illegible]0	Normal	0.80	0.26	0.14	780
H. S.	Normal	F	5	Normal	104/60	Normal	0.80	0.28	0.08	1,025
R. F.	Normal	M	17	Normal	115/60	Normal	0.90	0.30	0.10	600
L. H.	Normal	M	15	Normal	140/[illegible]	Normal	0.75	0.24	0.09	1,100

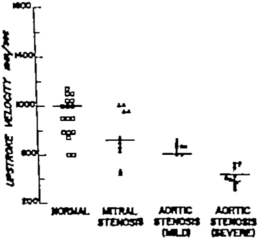


Fig 2 Upstroke velocity in normal patients and patients with mitral stenosis mild aortic stenosis and severe aortic stenosis The lines through the columns represent means for each group X Congenital aortic stenosis O Acquired aortic stenosis ● Combined aortic and mitral stenosis △ Mitral stenosis normal cardiac index ▲ Mitral stenosis low cardiac index

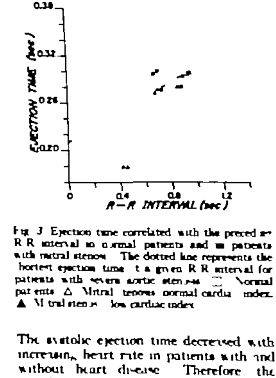


Fig 3 Ejection time correlated with the preceding R R interval in normal patients and in patients with mitral stenosis The dotted line represents the shortest ejection time at a given R R interval for patients with severe aortic stenosis □ Normal patients △ Mitral stenosis normal cardiac index ▲ Mitral stenosis low cardiac index

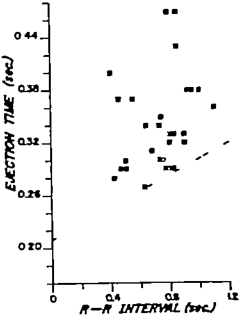


Fig 4 Ejection time correlated with the preceding R R interval in patients with aortic stenosis The dotted line represents the shortest ejection time at a given R R interval for patients with aortic stenosis ■ Severe aortic stenosis O Mild aortic stenosis acquired X Mild aortic stenosis congenital

The systolic ejection time decreased with increasing heart rate in patients with and without heart disease Therefore the systolic ejection time in patients with and without aortic stenosis must be compared at identical ventricular rates An arbitrary line connecting the shortest systolic ejection time for given rates in severe aortic stenosis has been drawn in Fig 3 From the slope of this line the shortest systolic ejection time for severe aortic stenosis for any given rate is determined by the formula Systolic ejection time = 0 092 (R R interval) + 0 21

Seven of the 40 patients without aortic stenosis had rate-correlated systolic ejection times in the range of those of patients with severe aortic obstruction One patient with acquired and 2 patients with congenital aortic stenosis who had mild disease had ejection times below the arbitrary range drawn for severe disease

Discussion

In a group of 20 patients with severe aortic stenosis Hancock and Abelman[7] noted an upstroke time of 0 14 to 0 24 second with a mean of 0 20 second Although they considered this mean to be significantly different from that of their patients without aortic stenosis there was an overlap in the range of values of their two groups Older normal patients tended to have a more prolonged brachial up-

stroke time but this was not so prolonged as that seen in patients with aortic stenosis Mathews and associates[9] reviewing 39 brachial arterial tracings (only 20 catheterized patients) found only one upstroke time of less than 0 15 second in severe aortic stenosis Hancock and Fleming[5] plotted brachial upstroke time against aortic valve areas and found no correlation However they did note that the upstroke time in patients with aortic stenosis was prolonged Lees and associates[10] and Braunwald and associates[11] in reviews of congenital aortic stenosis negated the importance of the direct brachial pressure pulse curves in the diagnosis of aortic obstructive *disease* *The results* presented in this paper however suggest that the brachial arterial upstroke time may be used effectively as a screening index for the absence or presence of severe acquired or congenital aortic valvular stenosis Only one patient without heart disease and one patient with mitral stenosis in a total of 40 patients had an upstroke time of 0 18 second or greater Only one of 24 patients with severe aortic stenosis had an upstroke time of less than 0 18 second An upstroke time of less than 0 18 second is highly suggestive of the absence of *severe* aortic valvular stenosis An upstroke time greater than 0 21 second was seen only in the group with severe aortic stenosis (12 of 24 patients)

In the group with mild aortic stenosis 8 of 9 patients with acquired stenosis had an upstroke time of 0 18 second or greater 6 of 7 patients with congenital stenosis had an upstroke time of less than 0 18 second An upstroke time of less than 0 10 second was seen only in patients without aortic valvular stenosis (8 patients with normal hearts and 6 patients with mitral stenosis) There was no significant correlation between the degree of prolongation of the upstroke time and the cardiac index A reduced cardiac index did not significantly change the upstroke time in either the group with mitral stenosis that with mild acquired aortic stenosis or that with severe aortic stenosis

Wood[3] described the brachial arterial upstroke velocity as an index for detecting the presence or absence of aortic stenosis His normal range was 750 to 1,250 mm Hg per second An upstroke velocity below 750 mm Hg per second would suggest aortic stenosis but he cautioned that patients with a decreased cardiac index may also have a decrease in the upstroke velocity In the present study the lowest upstroke velocity in normal subjects was 597 mm Hg per second Only one of 24 patients with severe aortic stenosis had an upstroke velocity greater than 600 mm Hg per second An upstroke velocity greater than 600 mm Hg per second is highly suggestive of the absence of *severe* aortic valvular disease Except for one patient with an aortic valve gradient of 45 mm Hg an upstroke velocity of less than 400 mm Hg per second was seen only in the group with severe aortic stenosis (13 of 24 patients) However 12 of 16 patients with mild aortic stenosis had upstroke velocities equal to or greater than 600 mm Hg per second One of the 2 patients with mild acquired aortic stenosis and an upstroke velocity of less than 600 mm Hg per second had a reduced cardiac index Only one of 7 patients with mitral stenosis and a normal cardiac index had an upstroke velocity of less than 600 mm Hg per second In patients with mitral stenosis with a decreased cardiac index 4 out of 11 had an upstroke velocity of less than 600 mm Hg per second which confirms Wood's observations of the relationship of cardiac index to upstroke velocity

An upstroke time greater than 0 21 second and/or an upstroke velocity of less than 400 mm Hg per second was seen in 16 of the 24 patients with severe aortic stenosis

The rate correlated systolic ejection time was the best of the three screening tests for the presence of obstruction of the aortic valve although it did not separate the group with mild aortic stenosis from the group with severe aortic stenosis

Since no one parameter was completely reliable for the evaluation of the severity of aortic stenosis all three measurements were cross analyzed The data indicated that the rate-correlated systolic ejection time was a good screening test for the presence of aortic stenosis regardless of the severity of the disease Only 3 of 16 patients with mild disease had ejection

times that were below the shortest rate correlated ejection time for severe aortic obstructive disease One of these 3 with a gradient of 20 mm had an upstroke time greater than 0 18 second (0 20 second) and an upstroke velocity of 600 mm Hg per second suggesting the presence of mild aortic stenosis A second patient with a gradient of 16 mm had an upstroke time of 0 18 second and an upstroke veloc ity of over 600 mm Hg per second again suggesting mild aortic stenosis The third patient had an upstroke time of 0 11 second and an upstroke velocity of over 600 mm Hg per second suggesting the absence of any aortic stenosis A cardiac angiogram showed deformity of the aortic valve No gradient across the aortic valve was noted

Thirteen patients with mild aortic ste nosis had rate correlated systolic ejection times in the range of those for severe aortic valvular obstruction A brachial arterial upstroke time of less than 0 18 second and or an upstroke velocity of over 600 mm Hg per second ruled out the presence of severe aortic stenosis in 11 of these patients The other 2 patients who had gradients of 30 and 45 mm Hg across the aortic valve could not be separated from the group with severe aortic stenosis

Seven of the 40 patients without aortic valvular stenosis had rate-correlated sys tolic ejection times in the range of those for severe aortic valvular obstruction A brachial arterial upstroke time of less than 0 18 second and/or an upstroke velocity greater than 600 mm Hg per second ruled out the presence of severe aortic stenosis in all 7 patients Two of these patients had upstroke times of less than 0 10 second suggesting the absence of any aortic stenosis The presence of mild aortic stenosis could not be excluded in the other 5 patients

The 4 of the 11 patients with mitral stenosis and diminished cardiac output who had upstroke velocities of less than 600 mm Hg per second would not be con sidered to have aortic stenosis because their upstroke times were less than 0 18 second and their rate-correlated systolic ejection times were normal

By means of these combined criteria there was complete separation of the 24 patients with severe aortic stenosis from the 40 patients without aortic obstructive disease By the same criteria there was good separation of the 16 patients with mild aortic stenosis from the 40 patients without aortic disease Thirty five of the 40 patients without aortic stenosis could be separated from the group with mild aortic stenosis Fifteen of the 16 patients with mild aortic stenosis could be sepa rated from the non aortic stenosis group The one patient with mild aortic stenosis who fell into the non aortic stenosis group had a clinically insignificant lesion Four teen of the 16 patients with mild aortic stenosis were also clearly separated from the 24 patients with severe aortic stenosis The 2 patients with mild aortic stenosis who fell into the group with severe aortic stenosis had gradients of 30 and 45 mm Hg across the valve at rest

Summary

An evaluation of the direct brachial arterial pressure pulse curve revealed that by analysis of the rate-correlated systolic ejection time the upstroke time and the upstroke velocity the presence of aortic valvular stenosis regardless of severity could be recognized with a high degree of accuracy In addition those patients with significant obstruction could be distin guished from those without significant disease

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Cardiovascular changes in tropical eosinophilia

A J Johny M B B S*
M D Ananthachari M D **
Trivandrum India

Tropical eosinophilia involves chiefly the respiratory system but several reports are on record which describe the atypical or aberrant manifestations of this syndrome involving the lymphatic gastrointestinal central nervous and cardiovascular systems and the skin There are very few reports in the literature which deal with cardiovascular involvement in tropical eosinophilia The earliest is that of Aubertin and Giroux[1] who detected a high eosinophil count (60 to 70 per cent) in a case of cardiac failure and atherosclerosis of the pulmonary artery Jhatakia[2] and Viswanathan[3] noted cases of tropical eosinophilia in which precordial pain simulating angina pectoris was a prominent symptom D Abrera[4] reported 2 cases of tropical eosinophilia one simulating rheumatic heart disease and the other rheumatic fever with carditis Misra and Prakash[5] reported the case of a patient with tropical eosinophilia who had also mitral stenosis and congestive cardiac failure Autopsy in this patient did not show any evidence of recent rheumatic infection Menon[6] reported the case of a patient with congestive cardiac failure and high eosinophil count who improved remarkably on diethylcarbamazine therapy

Vakil[7] in 1961 first stressed the existence of cardiovascular involvement in tropical eosinophilia mild and generally devoid of serious consequences which however may potentiate pre existing heart disease Thirty seven of his 100 cases showed evidence of cardiac involvement

Materials and methods

The present study is based on the observations made on 50 cases of tropical eosinophilia seen during a period of 1 year (1963 to 1964) in the Medical College Hospital Trivandrum Cases of tropical eosinophilia were selected for study when the following criteria were fulfilled (1) There was an absolute eosinophil count of more than 2 000 per cubic millimeter of blood (2) All known causes of blood eosinophilia such as parasitic infestations of the alimentary tract filariasis tuberculosis allergic disorders (such as bronchial asthma and urticaria) Hodgkin s disease and polyarteritis nodosa had been excluded (3) There was a definitive response to diethyl carbamazine therapy (4) There were predominant respiratory symptoms and signs and characteristic radiologic findings

Filarial complement fixation test could not be done in the present study

The age and sex distribution of the patients is shown in Table I The absolute eosinophil count varied from 2 050 to 48 800 per cubic millimeter of blood A standard 12 lead electrocardiogram (ECG) was taken in all patients before treatment was started The ECG was repeated on completion of treatment that is 10 days after the start of therapy and again 1

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*… of Postgraduate St d   Med c
**Director of Postgrad   St d   Medicine M d cal College Hospital T   drum K   l South Ind

Table I. Age and sex distribution of the patients

Age (yr.)	Males	Females	Total
0–9	—	—	—
10–19	9	—	9
20–29	16	1	17
30–39	11	2	13
40–49	2	4	6
50 and over	4	1	5
Total	4	8	50

Table II. Classification of ECG changes

Nature of electrocardiogram	Number of cases	
Disturbances in rate (sinus rhythm in all cases)		
Tachycardia (above 90)	8	13
Bradycardia (below 60)	5	
Disturbances in conduction		
First-degree A-V block	1	3
Incomplete right bundle branch block	2	
Relative ventricular preponderance and position of heart		
Clockwise rotation	10	14
Left ventricular hypertrophy	4	
Right ventricular hypertrophy	0	
Abnormalities of atrial complex		
Peaking of P waves with or without increased amplitude and/or duration	5	6
Bifid P wave	1	
Abnormalities of ventricular complex		
T wave abnormalities	6	8
S-T segment changes	2	
Changes suggestive of ischemia of the posterior wall of the ventricle	2	
Changes suggestive of chronic cor pulmonale	2	

month later. Patients were followed for periods of time that varied from 3 months to 1 year after discharge.

Results

In the present study, only 1 patient had symptoms and signs suggestive of congestive cardiac failure, and a diagnosis of chronic cor pulmonale resulting from long-standing tropical eosinophilia was made. With diethyl carbamazine therapy he showed only slight symptomatic improvement, probably because the changes in the lungs were irreversible. Twelve (24 per cent) patients complained of retrosternal discomfort. The discomfort was of a constant nature, not worsening on exertion nor showing any radiation characteristic of ischemic pain of cardiac origin. Physical examination of these patients did not show detectable valvular, myocardial, or pericardial involvement. The radiologic appearances were also within normal limits. Moreover, retrosternal discomfort was complained of by patients with no ECG abnormality.

The predominant observations were in the electrocardiograms of these patients. Most of the ECG changes were of mild to moderate degree and transient in nature. By the end of even 10 days, nearly all of the patients showed reversion of the ECG to near normality, in some, a completely normal pattern was restored. All patients except the one with chronic cor pulmonale showed a normal ECG pattern by the end of 1 month. Amelioration of respiratory symptoms and reversion of ECG changes to normality did not run parallel, the ECG changes taking a longer time to revert to normal. Table II shows the types of electrocardiograms observed. Of the 50 patients with tropical eosinophilia who were studied, 26 (52 per cent) showed some form of ECG abnormality.

The electrocardiograms showing abnormality were grouped according to the type of the cardiac involvement: *Group I*, with only abnormal rates of cardiac action; *Group II*, with disturbance of conduction, ventricular preponderance, and P wave changes; and *Group III*, S-T segment and T wave abnormalities. Of the 26 cases (52 per cent) with ECG changes, 6 (12 per cent) were included in Group I, 15 (30 per cent) in Group II, and 5 (10 per cent) in Group III.

The common ECG changes observed were: clockwise rotation, 10 cases; sinus tachycardia, 8 cases; T wave changes, 6 cases; sinus bradycardia, 5 cases; P wave changes, 5 cases; left ventricular hypertrophy, 4 cases.

Clockwise rotation observed in the present study was of a high degree (prominent or dominant S waves from Lead V_1 to Lead V_6). This change in the ECG often took a longer period to revert to normality than did the other changes.

The heart rate showed either an increase or decrease in 50 per cent of the patients the former being more common. With treatment the rate always showed a tendency toward normalcy.

Definite left ventricular hypertrophy according to the criteria of Sokolow and Lyon [8] was observed in 4 patients.

Peaking of the P waves was the common abnormality in the atrial complex (5 patients). In 2 patients the height of the P wave exceeded 3 mm. Bifid P wave suggestive of left atrial hypertrophy was seen in 1 patient but there was no evidence of mitral valve disease.

Marked T wave changes were seen in 6 patients. In 3 patients T wave inversion was symmetrical and in 1 a diagnosis of posterior wall ischemia could well be deemed to be in order. Another patient showed flat T waves in the posterior leads suggesting ischemia of the posterior wall. Terminal inversion of T waves in the precordial leads was observed in 3 other patients. Case 1 had T waves which were abnormal both in height and shape in Leads L_I, L_{II}, aVF and V_6. These changes reverted to normal after treatment.

One patient showed S-T segment depression with T wave inversion. In another the S-T segment was elevated more than 1 mm but the concavity was upward. The T wave was normal.

The relationship of the incidence of ECG abnormality to the height of the blood eosinophil count, the duration of illness and the age of the patients is shown in Tables III, IV and V respectively.

Table III. Distribution of patients with ECG changes according to blood eosinophil count

Eosinophil count (per cu. mm. of blood)	*Number of patients*	*Number of patients with ECG changes*	*Percentage of incidence of ECG changes*
Less than 2 000	5	1	0
2 000 to 5 000	16	5	31
5 000 to 10 000	11	6	55
10 000 to 20 000	11	8	43
20 000 to 40 000	5	4	80
Over 40 000	2	2	100
Total	50	26	5

Table IV. Distribution of patients with ECG changes according to duration of illness

Duration of illness	*Number of patients*	*Number of patients with ECG changes*	*Percentage of incidence of ECG changes*
Less than 1 mo.	9	2	22
1 to 6 mo.	19	10	53
6 to 12 mo.	6	4	67
1 to 4 yr.	14	9	66
Over 4 yr.		1	50
Total	50	26	52

Table V. Distribution of patients with ECG changes according to the age of the patients

Age group (yr.)	*Number of patients*	*Number of patients with ECG changes*	*Percentage of incidence of ECG changes*
10–19	9	6	67
20–29	17	7	41
30–39	13	7	54
40–49	6	2	33
Over 50	5	4	80
Total	50	26	52

Illustrative cases

Case 1. A 16-year-old boy was hospitalized because of complaints of paroxysmal nocturnal cough which had been present for 1½ months. Six months earlier he had had a similar attack which had lasted for 1 month. He had noticed gradual loss of weight over the past 1 year. The blood count showed 27 000 eosinophil per cubic millimeter; the erythrocyte sedimentation rate was 7 mm. in the first hour. A skiagram of the chest showed bilateral diffuse soft mottling and prominent hilar shadows. A liver biopsy showed eosinophilic aggregations microscopically.

An ECG taken prior to treatment showed abnormally tall (8.5 mm.) and abnormally shaped T waves in L_I, L_{II}, aVF and V_6. The ECG taken after treatment showed changes toward a normal pattern (see Fig. 1, *a* and *b*). The third ECG taken 1 month after full treatment with the patient free of symptoms showed a normal pattern.

Case 2. A 28-year-old woman was hospitalized because of proxysmal nocturnal cough followed by an asthmatic type of dyspnea which had been present for 8 days. She had pain on both sides of the chest, more over the precordium, but not suggestive of cardiac ischemia.

The ECG pattern before treatment was like that seen in the case of old posterolateral infarction. With therapy the record reverted to a

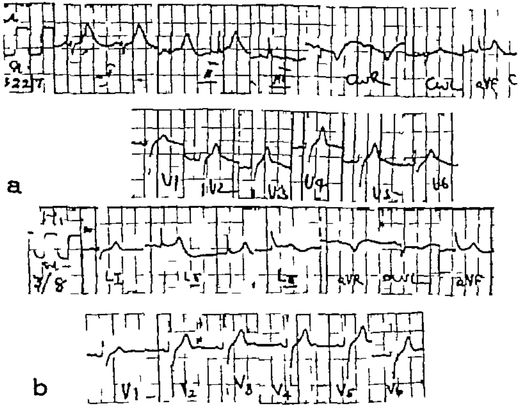


Fig. 1. *a*, Note the abnormally tall and abnormally shaped T waves in Leads I, II, aVF, and V and reciprocally deeply inverted T of abnormal shape in aVR. *b*, Note the reversion toward a normal ECG pattern in the same patient after 10 days of treatment.

tern within a period of 10 days (see Fig. 2, *a* and *b*).

Case 3. A 42 year-old woman was hospitalized because of cough and an asthmatic type of dyspnea. There was no history suggestive of myocardial ischemia. The ECG showed evidence of ischemia of the posterior wall (Fig. 3). *The records on completion* of treatment showed a normal pattern.

Case 4. A 50 year-old man was hospitalized because of expiratory dyspnea, paroxysmal nocturnal cough, and pain in the right inframaxillary area, all of which had been present for 4 months. The blood count showed 48,000 eosinophils per cubic millimeter. A skiagram of the chest showed bilateral mottling and a dense shadow with early breaking down in the center in the right lower lobe.

The ECG showed T wave changes in all leads simulating myocardial ischemia. The second record taken after treatment showed changes toward a normal pattern. The ECG taken 1 month later was normal (Fig. 4, *a*, *b*, and).

Case 5. A 58 year-old man was hospitalized because of symptoms and signs suggestive of chronic cor pulmonale. The duration of illness had been 21 years. The ECG showed peaked P waves (Fig. 5). The cardiac changes remained unaltered even after treatment.

Discussion

Even in this small number of 50 cases of tropical eosinophilia, 52 per cent showed indisputably abnormal ECG patterns. The fact that these changes reverted to a normal pattern with treatment points to a cause and effect relationship of a degree *which is more than can be attributed* to chance. Furthermore, this study reveals that the relationship of the incidence of ECG changes to the degree of eosinophilia (more than 40,000) is beyond the range of coincidence. Table III suggests a definite relationship between eosinophil count and percentage incidence of cardiac abnormality (after test standardization for the difference in the number of patients). The duration of the illness is not so significant as is the eosinophil count. Vakil's[7] observation is not in agreement with this. He noted no relationship between the cardiac involvement and the level of eosinophilia. However, he observed that ECG changes *were more frequent in* cases of long duration and in cases in which there was preexisting heart disease. Table V shows that there is no age liability to cardiac abnormality. Moreover, the severe ST and

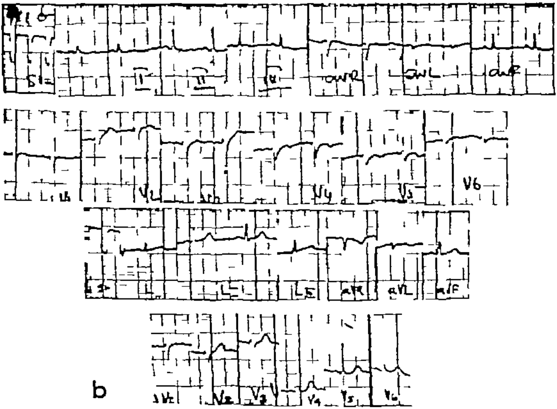


Fig. 2 a Note the inverted T waves in Lead II III and aVF and the terminal inversion of T waves in V [illegible] V [illegible] and V[illegible]. b Note the normal ECG pattern of the same patient after 10 days of treatment

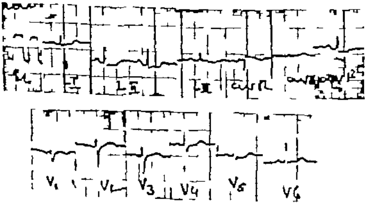


Fig. 3 Note the inverted T waves in Leads II III and aVF suggestive of posterior wall ischemia.

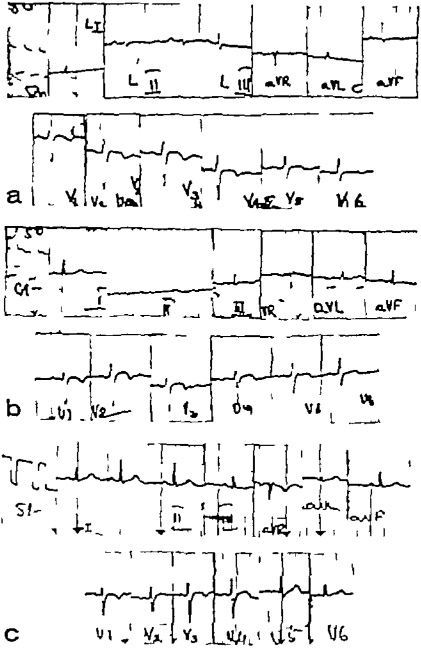


Fig. 4. a, Note the T wave abnormalities in the chest and precordial leads. b, Note the upright T wave in Lead I after 10 days of treatment. c, Note the normal ECG pattern at the end of 1 month.

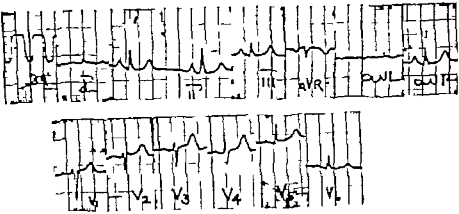


Fig 5 Note the peaked P wave

T changes were observed in both young and old patients so that a contributory pre existent atherosclerosis of the coronary artery could be excluded Furthermore T wave inversion of ischemic origin reverts to normal only after many months[9] In the present study these T wave changes reverted to normal pattern within a short period of 10 days

The heart rate showed either an increase or decrease in 50 per cent of the patients With treatment the rate always showed a tendency toward normalcy This feature is in accord with the supposition that myocardial abnormality is incidental to tropical eosinophilia Although abnormal rate by itself may not mean much in conjunction with other evidence of myocardial changes it is highly suggestive of a direct relationship of the disease to the myocardial damage

Because of the fact that 4 patients showed definite left ventricular hypertrophy it seems that tropical eosinophilia can result in ventricular preponderance as an indication of a form of myocarditis

It is difficult to assess the significance of the P wave changes seen in the present study P wave abnormalities of like nature are traditionally taken as indicative of atrial hypertrophy[9] Although various forms of myocarditis are known to result in ventricular hypertrophies such changes have not been known to follow in the atria Hence the significance of these changes requires further study

Various observers of tropical eosinophilia emphasize one fact i e that the lesions of the disease tend to manifest as eosinophilic granulomatous aggregations in different organs perhaps predominantly in the lungs Webb[10] and Viswanathan[11] have made notable observations in this regard Few however have remarked upon the possibility of similar lesions in the myocardium This may be due to a paucity of postmortem study since tropical eosinophilia is seldom fatal and the obvious impossibility of biopsy study of the myocardium as a routine procedure Hence the observation of a 52 per cent incidence of tangible myocardial abnormality in this small number of cases is of real significance

It is accepted that the majority of these granulomatous changes ultimately resolve and tend to leave as evidence only fibrous tissue changes[10,11] This fact assumes importance when one considers the possible origin of changes in the myocardium noted in this study

The following facts stand out Abnormalities of pattern in the ECG greatly simulating ischemic disease reverted to normal within a short period of treatment Such a return to normal will not be expected to occur with healed granulomatous lesions (fibrosis) characteristic of tropical eosinophilia that are seen in other organs such as the lung liver and lymph glands The most likely explanation is that the nature of the damage is not permanent and probably not similar Functional disturbance *in cardiac action evidenced* only by abnormalities of rate particularly bradycardia would lend support to the

notion that tropical eosinophilia can produce a toxic type of functional defect

Various nonspecific myocardial reactions which result in hypertrophy of the musculature are generally grouped under cardiomyopathy or nonspecific myocarditis Hypertrophy of the ventricles without obvious work load in the circulation is noted in these cases Among the patients under study 4 showed definite ECG patterns of left ventricular hypertrophy which reverted to normal although slowly concurrently with cure of the symptoms This is understandable if the suggestion that tropical eosinophilia may have a toxic manifestation is accepted However what is not easily explained is the finding of an ECG abnormality that suggests atrial hypertrophy (except in the one patient who had clinical cor pulmonale and in whom reversion of the ECG to normal did not take place with treatment which emphasizes that this patient had pulmonary causes to account for the cor pulmonale and P wave changes)

It is evident that tropical eosinophilia is not just a disease with no fatality or one in which the etiological factor is still [un]discerned More important it would seem is the possibility of this syndrome having its effect upon the myocardium the significance of which will have to be assessed in the manner one would in cases of emetine therapy

Summary

Fifty cases of tropical eosinophilia were studied in order to note the cardiovascular involvement with special reference to ECG changes Significant changes were noted in 52 per cent of the cases The possible relationship of tropical eosinophilia to the myocardial changes are discussed

We wish to express our thanks to Dr P M Kasu Assistant Professor of Medicine for his valuable help in the preparation of this paper as well as to Dr K N Iai Professor of Medicine for his guidance the Superintendent of the Hospital for permitting us to publish the hospital records and Mr Raman College Statistician for his help in the analysis of the tables

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Overlapping of ventricular filling and contraction

William Dressler, M.D.
*Richard Rubin, M.D.***
Brooklyn, N. Y.

Filling of the ventricle is known to occur during the diastolic phase. There are exceptional cases in which filling and contraction of the ventricle are overlapping. Examples of this seemingly paradoxical phenomenon are reported here.

1. Mitral regurgitation with rapid ventricular filling occurring in early systole after a short diastole.

CASE 1. G. W., a 26-year-old man, was admitted to the Maimonides Hospital in May, 1964, because of shortness of breath. He had suffered rheumatic fever when he was 10 years old, and valvular heart disease had been diagnosed at age 16. Exertional dyspnea was first felt in November, 1961. In the fall of 1962, the patient was treated for bacterial endocarditis. He recovered, but his complaints of dyspnea became worse.

Physical examination revealed marked respiratory distress. The blood pressure was 110/70 mm. Hg. The heart action was irregular, with a ventricular rate of 120 per minute. The cervical veins were not distended. Moist râles and rhonchi were heard over the lungs. The apex beat of the heart was felt in the fifth and sixth intercostal spaces, almost in the left anterior axillary line; it was broad and heaving in quality. A distinct shock was felt during diastole in the apical region, simultaneously with a loud third sound. In the left parasternal area, a heaving pulsation was observed during systole. In the apical region a loud blowing pansystolic murmur was heard which was transmitted to the left axilla. There was also a short diastolic murmur. The lower edge of the liver was felt 2 fingerbreadths below the right costal margin. The liver did not show a palpable pulsation.

The clinical diagnosis was rheumatic heart disease, with mitral regurgitation as the dominant lesion. Cineangiography and cardiac catheterization studies corroborated this diagnosis.

Phonocardiograms and apex cardiograms were taken (Fig. 1). The tracing showed an irregular heart action which was due to atrial fibrillation. A pansystolic murmur was most distinct after long diastoles. In Fig. 1, *A*, the third heart sound is the loudest of all the sounds. It follows the second sound after a pause of 0.14 second. Synchronous with the third sound is an early diastolic peak in the apex cardiogram, which obviously represents the ventricular knock[1] of marked mitral regurgitation. After the third heartbeat, diastole is short and the ventricular knock is inscribed on the ascending limb of the following apex cardiogram. The corresponding third heart sound is louder than in the preceding beats. The first sound of the last ventricular beat is delayed, coming 0.065 second after the onset of the ventricular contraction, whereas the corresponding interval in the other beats measures 0.04 second.

From the Department of Medicine, Maimonides Hospital of Brooklyn, Brooklyn, N. Y.
Received for publication on July 2, 1964.
Address: Maimonides Hospital of Brooklyn, 4802 Tenth Ave., Brooklyn 19, N. Y.
**National Institutes of Health Postdoctoral Research Fellow.

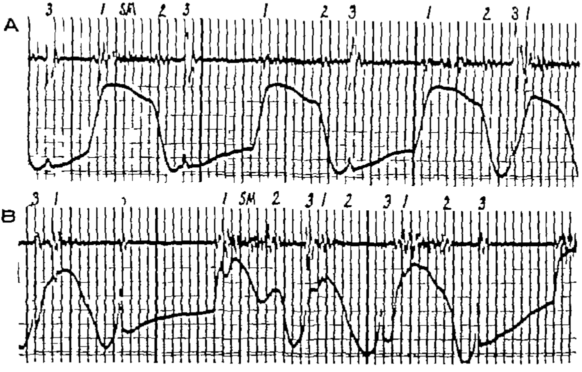


Fig. 1. Case 1. Mitral regurgitation with atrial fibrillation. Above is the phonocardiogram, below is the apex cardiogram. A loud third sound is seen which is synchronous with a ventricular knock in the apex cardiogram. In tracing A the third sound is louder than all other sounds. There is a very short diastole in A after the third beat and in B after the second beat. The ventricular knock and corresponding third sound which follow the diastole fall in the ascending limb of the next ventricular contraction, and the first sound of these particular beats is delayed.

In Fig. 1 B the cardiac knock is huge after the second beat. Because of a short diastole, it is superimposed on the ascending limb of the apex cardiogram of the third ventricular contraction. The coinciding third sound is particularly loud. There is again a delay of the first sound, which arrives about 0.07 second after the onset of the third ventricular systole.

Comment. Case 1 represents marked mitral regurgitation with atrial fibrillation, loud third sound, and a sharp diastolic knock. After short diastoles rapid inflow into the ventricles does not take place until after the onset of the following ventricular contraction. The impact of the inrushing blood has a more forceful effect when it hits the firm wall of a contracted ventricle rather than the relaxed chamber during the diastolic phase. Hence, the peak signifying this impact in the apex cardiogram is huge and the corresponding third sound is of increased intensity.

In the beats which come after a very short diastole, the first sound is delayed by 0.02 to 0.03 second. The delay is explained by the fact that the ventricle is inadequately filled and has to labor against a higher pressure in the left atrium which could not empty its contents during the short diastole.

2. Diastolic murmur of aortic regurgitation extending into the following ventricular systole

CASE 2. Ch. C., a 77-year-old man, was first examined by one of us (W. D.) on May 2, 1963. He had suffered from high blood pressure for the previous 15 years. There was no history of rheumatic fever nor was the patient aware of having heart disease until recently. For the past 7 weeks he had felt tired and complained of shortness of breath. A diastolic murmur was heard in the aortic area. Two weeks prior to examination the patient became suddenly aware of a rasping sound in his chest. A loud diastolic murmur of musical character was audible all over the chest; it was

loudest in the right third intercostal space Serology was weakly positive Fluoroscopy revealed widening of the ascending aorta which showed large pulsatory excursions The left ventricle was moderately enlarged The blood pressure was 180/76 mm Hg The electrocardiogram showed the pattern of left ventricular hypertrophy and strain Syphilitic aortic regurgitation was thought to be present

Fig 2 shows a phonocardiogram taken from the right third intercostal space A musical diastolic murmur is noticed which begins at the second heart sound and extends throughout diastole into the first portion of the following ventricular systole This is most distinct in the first beat where the interval between onset of QRS and the end of the regurgitation murmur measures 0 12 second whereas closure of the atrioventricular valves in normal adults occurs 0 055 second after the onset of *QRS*

CASE 3 Ch F a 64 year old man was admitted to the Maimonides Hospital on March 20 1964 He complained chiefly of shortness of breath In 1938 he had been treated for bad blood with bismuth and arsenicals Since 1958 he had been hospitalized six times for treatment of congestive heart failure

Physical examination revealed a bounding arterial pulse The blood pressure on admission was 180 80 mm Hg Later readings ranged from 158/62 to 162/62 mm Hg The apical impulse of the heart was felt in the sixth intercostal space almost in the left anterior axillary line it was broad and of heaving quality A diastolic thrill was felt in the aortic area A loud diastolic murmur of musical character was best heard at the right sternal edge in the second and third intercostal spaces The liver was palpable 4 finger breadths below the right costal margin Serology was positive Syphilitic aortic

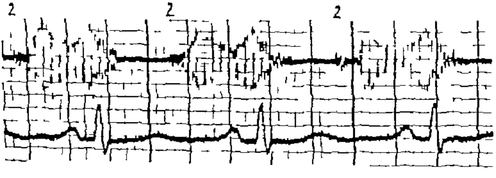


Fig 2 Case 2 Syphilitic aortic regurgitation The phonocardiogram (above) shows a musical diastolic murmur whose sharp outline and regular structure make it possible to recognize that the vibrations extend into the first part of ventricular systole For the first beat the interval between onset of the QRS and the end of the diastolic murmur measures 0 12 second

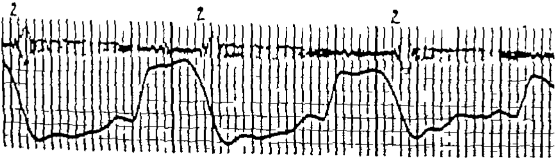


Fig 3 Syphilitic aortic regurgitation with long standing congestive heart failure *Above* Phonocardiogram *Below* Apex cardiogram There is a musical diastolic murmur which extends through diastole and about 0 04 second after the onset of ventricular contraction

regurgitation with congestive heart failure was diagnosed.

Fig. 3 shows a phonocardiogram taken from the right third intercostal space and an apex cardiogram. A diastolic murmur composed of sine waves is seen which starts at the second heart sound and extends 0.04 second beyond the foot of the apex cardiogram.

Comment. In Cases 2 and 3 a musical diastolic murmur of aortic regurgitation extended into the early portion of ventricular systole.

Discussion

The flow of blood is largely determined by the gradient of pressure. When the pressure in the left ventricle is lower than that in the aorta or left atrium, inflow of blood from these structures into the ventricle may take place even during the phase of systole. In aortic regurgitation, when the leak is not very large, an effective aorticoventricular gradient may be maintained not only during the whole of diastole, but also in the early portion of the following ventricular systole, prior to the ejection phase. In Cases 2 and 3, diastolic arterial pressures ranged from 60 to 72 mm. Hg. Thus an aortico-ventricular gradient above murmur threshold existed which extended into early ventricular systole. Hence regurgitation continued for a short while after the onset of ventricular contraction.

In the instance of marked mitral regurgitation, reduction in the duration of diastole prevented the atrium from emptying its contents during the early diastolic phase. Hence pressure in the left atrium remained high after the end of diastole, and rapid inflow of blood occurred in the early part of ventricular systole.

In the reported instances, recognition of inflow of blood into the contracted ventricle was facilitated by the presence of particular signs: in the cases of aortic regurgitation by the sharply defined outline of a characteristic musical murmur and in the instance of mitral regurgitation by a loud third sound and a synchronous peak in the graph of the apex beat denoting rapid ventricular filling.

Filling of the ventricle in early systole as observed in the instance of mitral regurgitation may be a mechanism by which circulation is maintained in the presence of rapid tachycardia with marked reduction in the duration of diastole.

Summary

Three cases are reported in which overlapping of ventricular filling and contraction was demonstrated by phonocardiograms and apex cardiograms.

In two instances of aortic regurgitation the sharply defined outline of a musical diastolic murmur signified that regurgitation extended into early ventricular systole.

In a case of mitral regurgitation with atrial fibrillation, rapid emptying of the atrium was marked by a third heart sound and a synchronous peak in the apex cardiogram. When diastole was short, the signs of rapid atrial emptying fell in the early part of the following ventricular systole. Significant associated features were an increase in the intensity of the third heart sound, a particularly forceful "ventricular knock," and delayed occurrence of the first heart sound.

Filling of the ventricle in early systole may be a mechanism by which circulation is maintained in the presence of tachycardia with marked shortening of the diastolic phase.

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The second heart sound in congenital pulmonary valvular insufficiency

*William J. Jacoby, Jr., Commander, MC, USN**
Donald H. Tucker, Lieutenant, MC, USNR
Robert G. Sumner, Lieutenant, MC, USNR
Portsmouth, Va.

A once rare anomaly, congenital pulmonary valvular insufficiency is now more frequently recognized. This apparently increased incidence can be attributed to a widespread appreciation of the characteristic clinical and laboratory features. Previous descriptions of the auscultatory and phonocardiographic findings have emphasized the diastolic murmur with only passing reference to the associated heart sounds. It is the purpose of this paper to focus attention on the second heart sound in pulmonary valvular insufficiency. Emphasis will be directed toward the resultant effects of anatomic and physiologic alterations on this sound. A review of the literature[1-3] and the study of 3 patients form the basis of this report.

Case reports

Case 1. †G. N., a 19-year-old white male, had first been noticed to have a heart murmur at the age of 6 years. He was asymptomatic and specifically denied any symptoms referable to the cardiovascular system.

Physical examination revealed a well-developed white male. The blood pressure was 120/70 mm. Hg and the pulse was 82 per minute. There was no cervical venous distention. The chest was symmetrical and the lungs were clear. A right ventricular lift was present and a systolic-diastolic thrill was palpable in the second left intercostal space. Normal sinus rhythm was noted. The first sound was normal and loudest at the apex. The second sound was of normal intensity and widely split throughout inspiration and expiration. A Grade 3/6 ejection systolic murmur and a Grade 3/6 decrescendo diastolic murmur were noted in the pulmonary area and along the left sternal border. Peripheral pulses were normal.

The electrocardiogram (Fig. 1) showed a right bundle branch block. The chest roentgenogram (Fig. 2,*A*) revealed right ventricular enlargement and marked dilatation of the pulmonary artery. The phonocardiogram (Fig. 3) demonstrated wide splitting (0.04 second) of the second heart sound in expiration with the pulmonary component delayed. A systolic and diastolic murmur was noted in the pulmonary area.

At catheterization (Table I) there was no evidence of intracardiac shunt demonstrated by a nitrous oxide test.[20] The pulmonary arterial pulse pressure was wide with a low diastolic pressure equal to that in the right ventricle. There was no significant systolic or diastolic pressure gradient from the pulmonary artery to the right ventricle. Indocyanine green dye dilution curves from the right ventricle to the brachial artery revealed a delayed downslope which in the absence of shunt was considered to be compatible with valvular insufficiency. Cineangiocardiograms demonstrated enlargement of the main pulmonary artery and regurgitation of dye from the pulmonary artery into the right ventricle, which established the diagnosis of pulmonary valvular insufficiency.

Case 2. N. P., an asymptomatic 21-year-old white male, had no previous history of cardiovascular disease.

From the Cardiopulmonary Laboratory, United States Naval Hospital, Portsmouth, Va.
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Received for publication July 6, 1964.
*Address: United States Naval Hospital, Great Lakes, Ill.
†This case [illegible]

Table I Catheterization data

	Pressures (mm Hg)				Hist ear angle test (°C)
	Right atrium	Right ventricle	Pulmonary artery	Brachial artery	
Case 1	(2)	37/6	28/6	122/77	5 0
Case 2	(3)	21 2	1 /3	126/64	8 7
Case 3	(0)	21/0	11/0	—	5 3

*Mean pressure

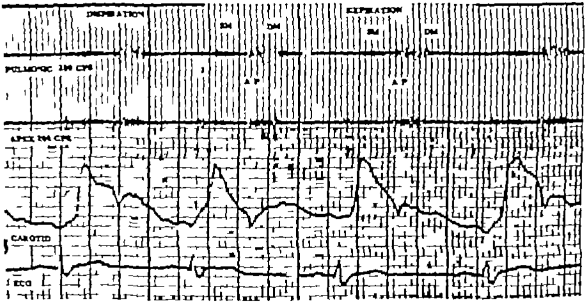


Fig 3 Case 1 Phonocardiogram The aortic (A) and pulmonary (P) components of the second heart sound are widely split in inspiration and expiration Systolic and diastolic murmur are noted with the latter beginning after the pulmonary component

trated a dilated pulmonary artery and pulmonary valvular regurgitation Contrast material injected into the root of the aorta revealed a competent aortic valve

Discussion

The normal relationship of the aortic and pulmonary components of the second heart sound and the effect of respiration have been emphasized by Leatham [3] Abnormalities of the semilunar valves the cardiac conduction system intravascular pressure and blood flow may produce an aberration of this relationship Congenital insufficiency of the pulmonary valve is the result of developmental anomalies which may produce alterations in the character of the second sound that are of diagnostic importance The second sound in this condition has been variously described as absent [1,4] single or diminished in intensity [7,8] abnormally split [10,11] and normal [10,11] A review of the cases reported in the literature prompted by the 3 cases described above suggests that anatomic and physiologic factors may explain the reported variability

The factors considered to be of importance in producing the alterations of the second sound in pulmonary regurgitation are the anatomy of the pulmonary valve the degree of dilatation of the pulmonary artery the volume of diastolic overload of the right ventricle the delayed activation

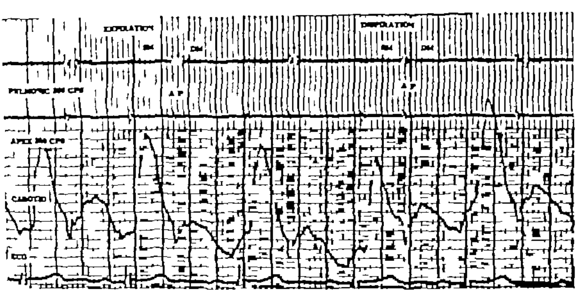


Fig. 4. Case 2. Phonocardiogram. The aortic (*A*) and pulmonary (*P*) components of the second heart sound are widely split (0.04 second) *in expiration with minimally increased* (0.02 second) variation in inspiration (0.06 second). A systolic and diastolic murmur were noted.

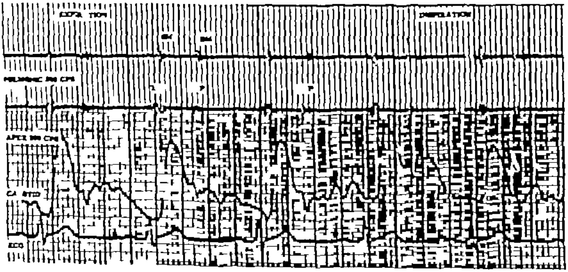


Fig. 5. Case 3. Phonocardiogram. The aortic (*A*) and pulmonary (*P*) components are widely split (0.05 second) in expiration with minimally increased (0.01 second) variation in inspiration (0.06 second). A systolic and diastolic murmur were noted.

of the right ventricle due to a conduction disturbance and associated congenital or acquired defects.

The prime requisite for production of the pulmonary component of the second sound is an anatomic pulmonary valve. Absence of the valve or small rudimentary cusps usually results in a single second sound. Experimental production of pulmonary insufficiency by surgical removal of the valve has been proved phonocardiographically to eliminate the pulmonary component.[8] In anatomic case descriptions of absent or rudimentary cusps the second sound is described as single or absent in the pulmonary area.[3,4]

Idiopathic dilatation of the pulmonary artery has been an anatomic and roentgen

Treatment of hypertension with methyldopa alone or combined with diuretics and/or guanethidine

A report of 63 cases

*Joseph W. Leonard, M.D.**
Ray W. Gifford, Jr., M.D.
David C. Humphrey, M.D.
Cleveland, Ohio

The antihypertensive effect of methyldopa is well documented.[1-6] A lowering of the supine blood pressure, usually without marked orthostatic or exertional hypotension, is particularly advantageous. Enhancement of antihypertensive effect both in the supine and in the standing positions is achieved by the combination of methyldopa and hydrochlorothiazide.[6] It has been suggested that guanethidine may be combined with methyldopa, and comparisons of the effects of each agent have been reported.[7-11] Hamilton[6] found that the antihypertensive effect of methyldopa is potentiated by guanethidine and suggested the use of the latter drug to overcome the tolerance sometimes seen during methyldopa therapy.

As *experience with methyldopa grows* the number of side effects attributed to it increases. Those mentioned include drowsiness, lethargy, headache, dry mouth, nausea, vomiting, diarrhea, faintness, nightmares, sexual impotence, retention of fluid, angina pectoris, changes in values in liver function tests, lactation,[1] Parkinsonism,[11] depression,[1,2] and fever.[16,17]

This report summarizes our experience with 63 patients treated with methyldopa† for periods up to 2 years and emphasizes the use of methyldopa in combination with guanethidine.

Methods and material

Sixty-five hypertensive patients were chosen for this study because they were considered to be cooperative and could either take their own blood pressures at home or could be seen at frequent intervals in the Clinic. Two patients failed to return after the initial evaluation and commencement of therapy. Records of 63 patients were adequate for evaluation of side effects, and 50 patients were studied for long enough periods to determine the *effects of methyldopa on their blood pres*sures. All patients were examined and were followed by the authors. Each patient underwent the usual laboratory and roentgenographic studies for evaluation of the cardiac and renal functions and in a search for curable causes of hypertension. In selected patients these studies included renal angiography and/or renal biopsy.

From the Department of Hypertension and Renal Disease, The Cleveland Clinic [illegible], Cleveland, Ohio.
Received for publication July 6, 1964.
*Formerly [illegible] Cleveland Clinic [illegible] Cleveland 6, Ohio. [illegible]
†[illegible] through the courtesy of Merck Sharp & Dohme, West Point, Pa.

Ages of the entire group ranged from 20 to 76 years. 29 patients were less than 50 years of age. There were 34 men and 29 women. The duration of hypertension ranged from less than 1 year to more than 40 years. Pertinent clinical data are listed in Table I.

Treatment was usually started with a total dosage of from 500 to 1 000 mg of methyldopa given daily by mouth in divided doses. The largest daily total dosage was 4 000 mg. Twelve patients were treated for less than 1 month, 27 for from 1 to 12 months and 24 for from 12 to 24 months. The effects of various regimens were studied: methyldopa alone, methyldopa plus a diuretic, and methyldopa with guanethidine.

Whenever available, home determinations of blood pressure were used to evaluate results. Thirty-four patients took

Table I. Clinical data on the 63 patients who received methyldopa during the study

Data	*Number of patients*
Type of hypertension	
Essential	51
Renal arterial stenosis	6
Chronic glomerulonephritis	4
Chronic pyelonephritis	2
Retinal findings (Keith-Wagener)	
Group 1	4
2	45
2+ (with retinal hemorrhages)	5
3	7
4	2
Cardiac status	
Normal	18
Angina pectoris	9
Congestive failure	8
Cardiac enlargement on roentgenogram	19
Electrocardiographic abnormalities	
Left ventricular hypertrophy	17
Non-specific ST-T abnormalities	9
Left ventricular preponderance	5
Myocardial infarction	3
Bundle branch block	1
Cerebral status	
Normal	58
Remote infarction	3
Intermittent insufficiency	3
Blood urea (mg./100 ml.)	
< 50	50
51-100	11
> 100	1

their blood pressures at home, repeating the determinations over a period of from 3 days to 1 month in order to obtain a control value while not taking antipressor medication. For 10 of these patients a control period was obtained in the hospital, and for only 1 patient were office-determined blood pressures compared with home readings. For 5 patients it was not deemed advisable to stop previous therapy before starting methyldopa.

Blood pressures determined at the Clinic were used for evaluation in the remainder of the patients. Recordings were made on at least three separate occasions before adding methyldopa to the regimen. Five patients received placebos during the control period.

All readings for the last month of any given period of observation were averaged to obtain the figures presented in the tables. For patients treated 1 month or less, all readings during the period of treatment were averaged. Unless otherwise stated, blood pressures recorded in the tables were taken while the patient was sitting.

Results

Treatment with methyldopa alone. The antihypertensive effects of methyldopa when administered as the sole agent to 16 patients are summarized in Table II. It is apparent that methyldopa has a moderately antihypertensive effect in the dosages used. In 1 patient there was no response. For 9 patients the addition of a diuretic after from 2 weeks to 5½ months was necessary to achieve additional antihypertensive effect.

In Table III are data from the records of 12 patients whose blood pressures were recorded in three positions at regular intervals throughout the study. When given as a sole agent, methyldopa exerted a significant antihypertensive effect in the supine position and only a slightly greater effect in the standing position. The addition of a diuretic enhanced the responses in all three positions.

Combined therapy with methyldopa. The antihypertensive responses of 8 patients who received methyldopa combined with an oral diuretic are summarized in Table IV. The addition of a diuretic effected

Table II Data showing antihypertensive effect of methyldopa when given as sole agent

Data obtained	Number of patients	Dose of methyldopa (mg)			Average BP (mm Hg)	
		High	Low	Av	Before therapy	During therapy
Last month of therapy	16	3 000	1 000	1 869	191/117	164/104
Therapy for more than 2 months during						
First month	9	3 000	500	1 295	187/117	156/102
Last month		3 000	1 500	1 888	187/117	159/99

*Mean blood p es = $\frac{Sy\ l\ + d\ st\ l}{2}$

Table III Data showing effect of posture on blood pressure of patients during treatment with methyldopa

Regimen	Number of patients	Blood pressure (mm Hg)					
		Supine		Sitting		Standing	
		Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy
Methyldopa alone	12	208/118	177/103	196/119	161/103	192/121	156/101
Methyldopa alone		210/116	174/100	202/117	165/107	199/118	163/102
Methyldopa and diuretic		210/116	157/93	202/117	144/89	199/118	142/90

Bl od pre su es were t ke d at th Cl ‖ except 1 pat ent

Table IV Data showing antihypertensive effect of methyldopa alone and in combination with

Therapy and when data were obtained	Dose of methyldopa (mg)			Average BP (mm Hg)	
	High	Low	Av	Before therapy	During therapy
Methyldopa alone during last month	2 000	1 750	1 93?	189/114	160/99
Methyldopa and diuretic during first month	2 000	1 500	1 906	189/114	149/93
Methyldopa and diuretic during last month	2 000	250	1 281	189/114	145/91

Mean blood pressure = $\frac{syst\ l\ +\ diast\ lic}{2}$

Average reduction in mean BP (%)	*Number of patients showing reduction in mean BP (%)*			*Number of normotensive patients (BP <150/100 mm. Hg)*
	<10%	*10-20%*	*>20%*	
13	5 (31)	8 (50)	3 (19)	3
15	3 (33)	5 (56)	1 (11)	1
15	1 (11)	6 (67)	2 (22)	2

equal or better control of the blood pressure while permitting a 33 per cent reduction of the average dose of methyldopa. Table V shows that methyldopa caused additional antihypertensive effect for 16 patients previously on a diuretic regimen. Fig. 1 graphically demonstrates this combined therapy.

Methyldopa was added to the regimens of 20 patients who had severe hypertension that was suboptimally controlled with guanethidine. A diuretic was also administered to 15 of these patients both before and during treatment with methyldopa. Equal or better control of the blood pressure was achieved for 16 patients while the average dose of guanethidine was reduced by 36 per cent. Fig. 2 illustrates this combined therapy. Data on these patients are recorded in Table VI.

Side effects. Only 18 of the 63 patients experienced no side effects (Table VII). Others noted one or more of the side effects listed in Table VII and 15 patients had to discontinue therapy because of untoward responses. In addition to those listed the following symptoms were noted only once: generalized weakness, dry skin, bad dreams, chills, and congestive heart failure.

Tests of liver function were obtained in 40 patients, 26 of whom had normal values. The remainder exhibited various abnormalities that were detected from the fourth to forty-eighth week of therapy with methyldopa. No patient had symptoms attributable to hepatic dysfunction. The abnormalities encountered were an increase in serum alkaline phosphatase concentration, thymol turbidity, and sulfobromophthalein retention, the highest values being 6.7 Bodansky units, 10.4 units, and 22 per

oral diuretics in 8 patients

Average reduction in mean BP (%)	*Number of patients showing reduction in mean BP*			*Number of normotensive patients (BP <150/100 mm. Hg)*
	<10%	*10-20%*	*>20%*	
15	2	4	2	0
21	0	2	6	3
22	1	4	3	5

Table V Data showing antihypertensive effect of methyldopa when added to diuretic regimen

Therapy	Dose of methyldopa (mg) High	Low	Av	Average BP (mm Hg) Before therapy	After therapy
Diuretic alone	—	—	—	193/117	168/108
Combined therapy during					
First month	1 250	500	765	193/117	154/99
Last month	2 000	500	1 050	193/11	147/9[illegible]

[illegible] blood pressure = (systolic + diastolic) / 2

†One patient received combined therapy for [illegible] months

Table VI Data showing effect of methyldopa and guanethidine in 20 patients

Average dose of guanethidine (mg/day)	Original regimen: Average BP (mm Hg) Sitting	Standing	First month: Guanethidine (mg/day)	Methyldopa (mg/day)
99	18[illegible]/109	162/100	72	893

[illegible] regimen of 13 patients

rent respectively The patient with the most marked abnormality had diabetes mellitus with hepatomegaly and abnormal liver function before commencement of methyldopa therapy In this patient there was no progression of the hepatic dysfunction during 54 weeks of methyldopa therapy Two of the 6 patients with febrile reactions exhibited minor increases in the serum alkaline phosphatase concentration or in thymol turbidity or in sulfobromophthalein retention In another patient a liver biopsy specimen taken at the time of cholecystectomy during the sixtieth week of therapy was normal In no patient did liver function abnormalities show progression despite continued therapy nor was it necessary to stop therapy because of hepatic dysfunction

Reasons for stopping therapy The reasons for discontinuing therapy with methyldopa in 37 patients were side effects (15) lack of cooperation (9) inadequate control of blood pressure (4) no longer needed to control blood pressure (4) death (3) acute cholecystitis requiring operation (1) and bleeding duodenal ulcer (1) In neither of the last two mentioned instances did methyldopa complicate the management of the patients

During therapy there were 3 deaths One was due to acute myocardial infarction and one to cerebral hemorrhage both were confirmed by postmortem examination In the third case the patient had arteriosclerotic heart disease and died suddenly at home no autopsy was performed

The side effects that caused patients to stop taking the drug were drowsiness fever depression headache impotence bad dreams dry mouth orthostatic hypotension weakness diarrhea and dizziness

Tolerance In 6 cases it was necessary

of 16 patients

Average reduction in mean BP* (%)	Number of patients showing reduction in mean BP			Number of normotensive patients (BP <150/100 mm Hg)
	<10%	10–20%	>20%	
11	7	8	1	3
18	3	8	5	5
22	4	5	6	6

on methyldopa		Last month on methyldopa			
Average BP (mm Hg)		Guanethidine	Methyldopa	Average BP (mm Hg)	
Sitting	Standing	(mg/day)		Sitting	Standing
174/105	146/91	57*	1 222	174/103	147/92

to increase the dosage of methyldopa after from 1 to 5 months of therapy in an effort to maintain control of the blood pressure. Tolerance developed more frequently when methyldopa was the sole agent than when it was used in conjunction with an oral diuretic and/or guanethidine. In 2 of these patients methyldopa was discontinued because the blood pressure was not adequately controlled.

Comment

Methyldopa, a decarboxylase inhibitor, is a welcome addition to a growing list of antihypertensive drugs, for it reduces blood pressure in the supine position almost as much as in the standing position and therefore does not cause symptoms of orthostatic hypotension so frequently as do the ganglion blocking agents and guanethidine. On the other hand, the antihypertensive effect of methyldopa used alone is not so potent as that of ganglion blocking agents or guanethidine.

Our experience indicates that methyldopa when used alone exerts only a moderately antihypertensive effect comparable to that of oral diuretics or reserpine; furthermore, control of the blood pressure is often erratic, and tolerance to the antihypertensive effect of methyldopa is likely to develop. For these reasons we advocate that it be used in conjunction with an oral diuretic agent and/or guanethidine except in some patients with renal failure for whom oral diuretics are contraindicated. Although in general we have not been so impressed as have Cannon and colleagues with the potency of methyldopa used as the sole agent in managing severe and malignant hypertension, we have found that the hypertension of some patients with renal failure responds satisfactorily to therapy with this agent alone. As stated

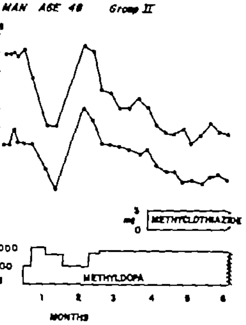


Fig. 1. Graph showing the blood pressure record of a 48-year-old man with essential hypertension, Group II. When used alone methyldopa controlled the blood pressure erratically and suboptimally, and tolerance gradually developed to the antihypertensive effect demonstrated initially. Addition of an oral diuretic (methyclothiazide) to the regimen stabilized the blood pressure at nearly normotensive level. (Because of several similar cases we no longer use methyldopa as the sole agent except in some patients with renal failure.)

Table VII. Side effects associated with methyldopa treatment in 63 patients

Side effects	Number of patients
None	18
Drowsiness	18
Abnormal liver function (*see text*)	14
Orthostatic weakness (usually in morning)	6
Fever	6
Dry mouth	6
Nasal stuffiness	5
Impotence	4
Diarrhea	4
Asymptomatic orthostatic fall in mean blood pressure of 15 mm. Hg	3
Dizziness	3
Pulse rate <62	2
Headache	2
Depression	2
Anorexia	2

Forty patients had tests of hepatic function.

by Cannon and co-workers: the fact that renal plasma flow is maintained when blood pressure is reduced by the administration of methyldopa makes it an especially attractive drug for the management of hypertension complicated by renal failure.

When hypertension is mild or only moderately severe (diastolic blood pressure is less than 125 mm. Hg) and the concentration of blood urea is normal, we initiate therapy with an oral diuretic and add a second agent after from 2 to 6 weeks if it appears that the hypertension is not adequately controlled. On the basis of the present study we prefer to add methyldopa when a second agent becomes necessary. Combination therapy with an oral diuretic and methyldopa (Tables IV and V) has a greater antihypertensive effect than that reported from combination therapy with an oral diuretic and either reserpine or hydralazine.[14]

Our study also demonstrated that methyldopa is effective when used in combina-

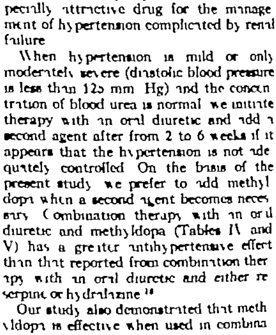


Fig. 2. Graph showing the monthly averages of home blood pressure recordings for a 46-year-old man with essential hypertension, Group II. The addition of methyldopa to his regimen permitted smoother control of the blood pressure with smaller doses of guanethidine and with lessening of the diurnal variation in blood pressure so commonly encountered during therapy with guanethidine.

tion with guanethidine with or without a diuretic in the management of severe hypertension. In some cases it was possible to control blood pressure with combination therapy after guanethidine alone or in conjunction with an oral diuretic had failed to do so. In nearly every case the addition of methyldopa to the regimen permitted an appreciable reduction in the dosage of guanethidine thereby reducing the number and severity of the side effects. Although the combination of methyldopa and guanethidine did not eliminate the morning orthostatic hypotension that so frequently was induced by therapy with guanethidine alone it ameliorated the afternoon hypertension in some cases. In our opinion the most potent antihypertensive regimen currently available consists of a combination of guanethidine methyldopa and an oral diuretic.

Several emotionally unstable patients of the 15 who stopped treatment because of side effects tolerated other antipressor drugs equally poorly and noted unusual and bizarre symptoms that were probably unrelated to therapy with methyldopa. Drowsiness which usually disappeared after the first 2 or 3 days of treatment was the most common side effect observed. Drug fever was the most serious side effect it forced abandonment of therapy in 3 patients.

In general methyldopa was well tolerated by most of the patients and it is our opinion that freedom from annoying and serious side effects is a distinct advantage of administering methyldopa as compared to the use of other antihypertensive agents except the oral diuretics. Abnormal results of liver function tests when occurring were minor and neither necessitated cessation of therapy in any case nor became worse with continued therapy. Worsening of angina pectoris as a result of therapy with methyldopa reported by Sheps and colleagues[7] was not observed in any of our patients and in some cases the reduction in blood pressure by treatment with methyldopa resulted in symptomatic improvement in angina pectoris.

Signs and symptoms of congestive heart failure appeared in 1 patient when methyldopa was added to an established regimen of guanethidine. Cardiac compensation was restored by treatment with digitalis and diuretics while therapy with methyldopa and guanethidine was continued.

This study has shed no light on the mechanism of the antihypertensive action of methyldopa. Sjoerdsma, Vendsalu and Engelman[18] presented evidence that indicates that its antihypertensive effect is unrelated to decarboxylase inhibition and results from depletion of tissue stores of catecholamines presumably mediated by amine metabolites of methyldopa.

Summary

Our experience in treating 63 hypertensive patients with methyldopa for periods up to 2 years reveals that it is a safe and effective antihypertensive drug especially when used in conjunction with an oral diuretic and or guanethidine. The average reduction in mean blood pressure achieved by therapy with methyldopa alone was 13 per cent and by combination therapy with methyldopa and an oral diuretic 22 per cent. The addition of methyldopa to the regimens of patients with severe hypertension permitted an improved control of blood pressure with reduced dosages of guanethidine in most cases.

Side effects although occurring frequently were usually well tolerated and not serious. Eighteen patients initially noted drowsiness which subsided despite continuance of therapy in most cases. Drug fever occurred in 6 patients 3 of whom were forced to discontinue treatment. Serious hepatotoxicity did not occur.

It is recommended that methyldopa be used in conjunction with an oral diuretic for patients with mild or moderate hypertension and in conjunction with guanethidine with or without an oral diuretic for patients with severe hypertension.

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The vectorcardiogram in children with left axis deviation and no apparent heart disease

*Alex M Gup Captain MC USA**
Robert B Franklin Colonel MC USA
John E Hill Jr Major MC USA
Denver Colo

It has long been known that left axis deviation occasionally occurs as a variant in children without apparent heart disease [1,2] The two most widely held theories explaining this variation are (a) that it is related to the anatomic position of the heart or (b) that it is caused by a conduction defect All previous studies that we have found in the literature in regard to this condition have been made with the use of the standard electrocardiogram In an attempt to better evaluate and explain left axis deviation in healthy children we have studied such a population with vectorcardiograms

Method

Electrocardiograms were obtained on 421 unselected children ranging in age from 4 to 13 years 54 per cent were females and 46 per cent were males The electrocardiograms of 3 girls and 3 boys (6 children 1 4 per cent) had mean QRS axes of less than −20 degrees and were considered as indicating left axis deviation After a 9 month interval follow up electrocardiograms were obtained on these 6 children The tracings were unchanged A medical history was obtained a complete physical examination was performed and posteroanterior and lateral x ray views of the chest were obtained in each child All of the children were found to be in good health and without any evidence of heart disease In addition vectorcardiograms using both the cube and Frank systems were recorded on each child

Results

The initial 0 04 second forces of the vectorcardiograms (qualitative analysis) followed normal and typical patterns In all except one case (Fig 3) the horizontal mean maximal vectors similarly remained within normal limits lying fairly close to zero degrees

The frontal loop was located superiorly and to the left with the discrepancy between loop and scalar axis being explained by Burger s observations [3] The sagittal loop showed anteroposterior orientation and a superior position with the initial forces tending to be in an anterior inferior position and the terminal forces in a posterior-superior position The terminal forces were invariably oriented posteriorly and somewhat superiorly and were invariably slowed (See Figs 1 6)

Discussion

Despite the fact that no completely satisfactory explanation for left axis deviation in children has been made physicians attach great importance to such a finding

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* Cardiology Service Department of Medicine Fitzsimons General Hospital Denver Colo
**Chief Cardiology Service Department of Medicine Fitzsimons General Hospital Denver Colo
Address correspondence to Capt Alex M Gup 1813 Whitney Ave Pensacola Fla [illegible]

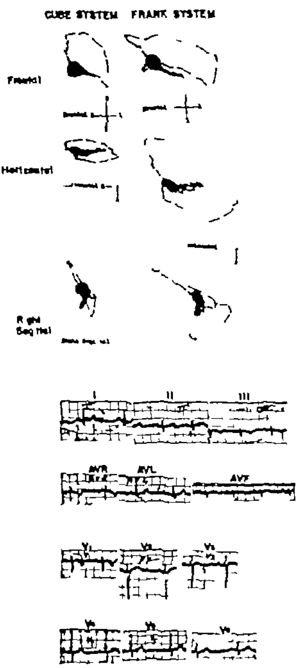


Fig. 1. I. I. female 11 years old

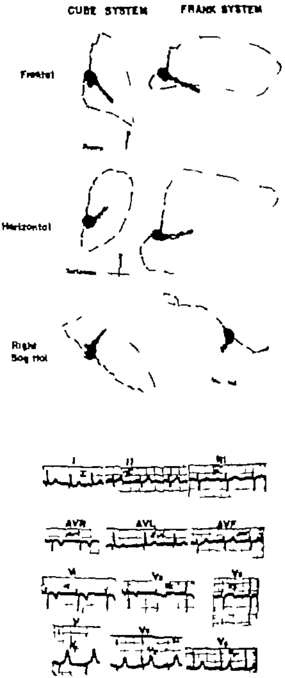


Fig. 2. C. S. male 8 years old

Occasionally left axis deviation occurs as a variant in children without apparent heart disease.

The standard electrocardiograms recorded on the 6 such children in our study showed no delay in QRS conduction, which ranged from 0.04 to 0.08 second. By analogy with Grant's study of parietal block[7] and Lev's study of conduction in atrioventricularis communis,[8] a defect in the superior branch of the left bundle with excitation of the high lateral and posterolateral walls of the left ventricle coming from the inferior branch via the myocardium is suggested.

Vectorcardiograms recorded on these

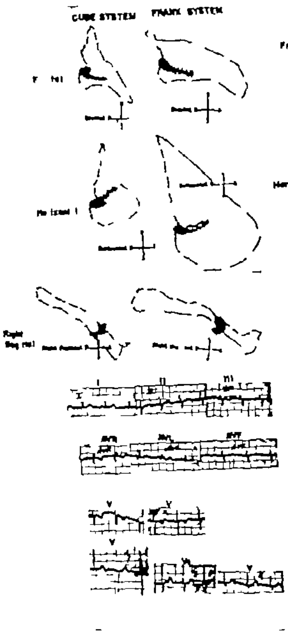


Fig. 3 D.D. male, 9 years old

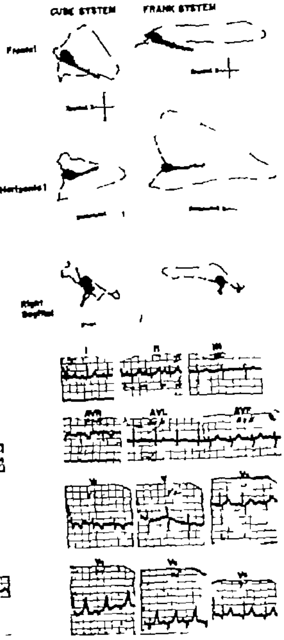


Fig. 4 L.B. female, 7 years old

children revealed the initial forces to be normal. The terminal forces were invariably rotated posteriorly and often superiorly. If one considers Scher's study of myocardial depolarization by intramyocardial electrodes in the dog, the terminal forces refer to excitation of the high posterior septum (the excitation ascending from the lower septum) and the high posterior free wall of the left ventricle (the excitation spreading via the terminal part of the electrical envelopment of the left ventricle).[8] It would seem, then, that the vectorcardiograms in our study show some delay in the excitation of these terminal areas. The presence of a conduction defect in the high posterior septum and the adjoining posterior wall of the left ventricle or a defective superior branch of the left bundle could explain this delay.

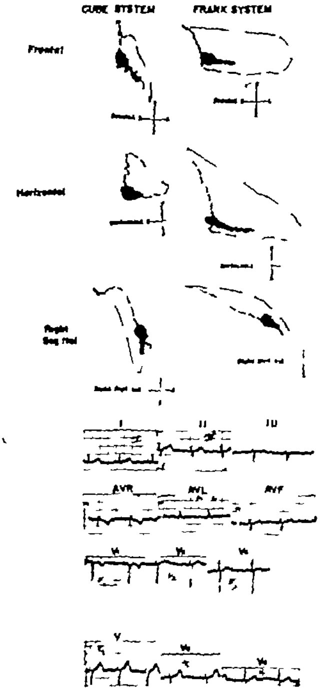


Fig. 5. M.L., male, 8 years old.

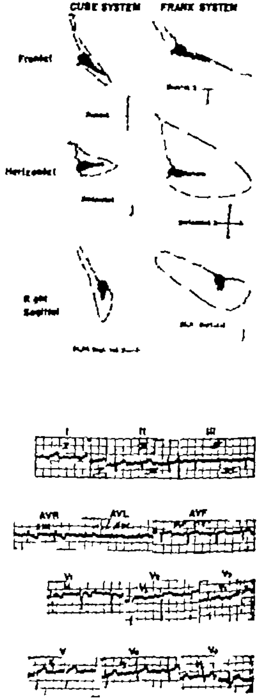


Fig. 6. T.S., female, 11 years old.

Some authorities believe that the position of the heart in the thorax may produce left axis deviation. Earlier electrocardiographic theories held that when the long axis of the normal heart is horizontal the left and right ventricles are so placed that the variations in potential of the left ventricle are transmitted to the left upper extremity. Thus, qR and rS complexes are seen in Lead aVL and aVF, respectively. This reasoning seems to be redundant since, in order to meet the criteria for left axis deviation, the standard electrocardiogram must reveal a hori-

zontal position of the heart. It also assumes that the anatomic and the electrical heart axes are closely related. This is not always a valid assumption.

A more satisfactory explanation for left axis deviation is the presence of a ventricular conduction defect. The left main bundle divides into superior and inferior branches. Ordinarily conduction spreads simultaneously through both branches. If part of the superior branch is blocked, however, activation would be started by the inferior branch, spreading from inferior to superior regions and tending to have a left ward direction. Left axis deviation would result. Because the block is peripheral, the QRS duration would remain within normal limits.

This same phenomena might also result from an abnormal course of the superior branch's peripheral distribution, with the activation being initiated in the low anterior septum and consequently a longer period required for transmission of the excitation wave to the upper septum and posterior ventricular free wall.

Conclusion

In an electrocardiographic survey of 421 unselected children, 6 (1.4 per cent) were discovered to have left axis deviation. After thorough evaluation, these 6 children were found to be in good health and without evidence of heart disease. Vectorcardiograms using the cube and Frank systems were recorded on each child. These vectorcardiograms suggested that the left axis deviation is caused by a delay in the terminal portion of the loop, perhaps due to a defect in the conduction of excitation through either the superior branch of the left bundle or the ventricular septum.

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Experimental and laboratory reports

Influence of ventricular size on the relationship between contractile and manifest tension

*George E. Burch, M.D.**
Nicholas P. DePasquale, M.D.
James A. Cronvich, M.S.
New Orleans, La.

The relationship between tension and pressure and volume (radius) of the ventricle is not always considered in discussions of the heart as a pump. However, by applying Laplace's law, the time course of tension can be calculated if the variations in pressure and volume during the cardiac cycle are known.[1] Recent experiments in which tension was measured directly have confirmed predictions based on the law.

According to Laplace's law, all else remaining constant, the tension in the wall of a sphere varies directly with the radius. Thus, if the left ventricle is considered to be spherical, the tension in the wall of a dilated ventricle would be greater than the tension in the wall of a normal sized ventricle for a given intraventricular pressure. Although the tension increases as the radius increases, the influence of the wall tension on the blood pressure within the ventricle does not increase, but rather decreases as the radius increases. It is necessary to distinguish between the tension of the contracting fibers of the myocardium which produce forces which act tangentially to the intraventricular cavity and the manifested (effective) tension which results from the wall tension and acts radially in the intraventricular cavity (Fig. 1) and is equal to the intraventricular pressure. It is the manifest or effective tension which is hemodynamically important rather than the tension in the wall itself. Because this aspect of Laplace's law has received little consideration in cardiac studies, it was thought to be of interest to present briefly the manner in which the geometry of the ventricular wall may influence the relationship between wall tension and manifest tension.

In this discussion, tangentially acting forces developed within the wall of the ventricle during contraction are considered as *contractile tension* of myocardial tightening. The *manifest tension* or radially directed resultant force is the tension actually exerted against the blood within the ventricle as the result of the *contractile tension*. The manifest tension is equal to the intraventricular pressure (Fig. 1).

For convenience of presentation, the ventricle is considered to be a sphere, and the tangential vectors of contractile tension are represented as chords or tangents of the sphere. Thus, in Fig. 2, the vectors x and y represent the contractile tension

From the Department of Medicine, Tulane University School of Medicine, and the Charity Hospital of Louisiana, New Orleans, La.
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*Address: Department of Medicine, Tulane University School of Medicine, 1430 Tulane Ave., New Orleans, La. 70112.

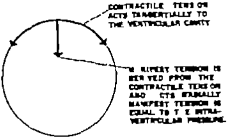


Fig 1

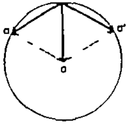


Fig 2

Fig 1 Relationship of contractile tension to manifest (effective) tension

Fig 2 Method of representing contractile tension a and a' as chords of a circle Manifest tension (a) can be obtained from a and a' or contractile tension (a,a') can be obtained from a by construction of a parallelogram of forces

and the vector a represents the manifest tension or resultant centrally directed force exerted against the blood in the ventricle Obviously these diagrams over simplify the situation because actually any elementary section of the sphere has forces directed in all directions but the tension in any direction is the vector sum of the many components

The ratio of the manifest tension to the contractile tension may be considered to be an expression of the efficiency of the tension developed by the contracting myocardium In Fig 3 the vectors a a and b b are of identical length However the resultant vector a derived from a a is greater than b derived from b b or stated differently the ratio a a is equal to 1 0 whereas the ratio b b is equal to 0 5 In order for the manifest force for the larger circle on the right hand side of Fig 3 to equal that of the smaller circle the tangential forces in the larger circle would have to be extended to c c i e essentially doubled in length

Fig 4 applies the above mentioned concept to the heart A normal sized heart with an end-diastolic volume of 100 c c is assumed to develop a contractile force of 2.8×10^4 dynes which results in a manifest tension (expressed as pressure) of 10.7×10^4 dynes/cm² which is just sufficient to open the aortic valve against a normal arterial diastolic pressure of 80 mm Hg (10.7×10^4 dynes cm²) On the other hand in the dilated heart with a 500 c c end-diastolic volume a contractile force of 2.8×10^4 dynes results in a manifest tension of 3.7×10^4 dynes cm which is not sufficient to open the aortic valve against a normal arterial diastolic pressure of 80 mm Hg (10.7×10^4 dynes cm) The lower portion of Fig 4 applies the same concepts to an arterial diastolic pressure of 120 mm Hg (16.0×10^4 dynes cm) with similar results Thus despite identical contractile tensions the resultant manifest tension is greater in the normal sized heart than in the dilated heart Therefore the dilated heart must exert greater contractile tension than the normal sized heart in order to produce the same manifest tension This effect is not related to the presence of myocardial disease per se but is purely a geometric consequence of dilatation and widening of the angle (hoop angle) between the vectors of contractile tension

These concepts are further illustrated

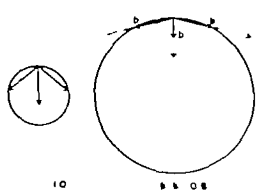


Fig 3 The vectors and for the small circle are of the same length as the vectors b and b of the large circle However the resultant or manifest vector ( ) is larger for the smaller circle than that (b) for the larger circle an unavoidable consequence of the differences in orientation of a,a and b b

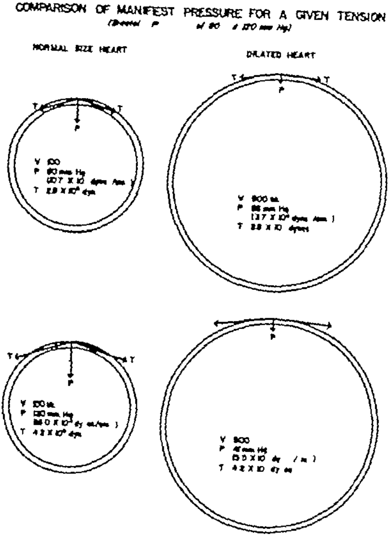


Fig. 4. The normal sized heart is assumed to develop a contractile force of 8 × 10⁶ dynes during isometric contraction which is sufficient to open the semilunar valves against a diastolic arterial pressure of 80 mm. Hg. On the other hand, the same contractile force in the dilated heart would not have been sufficient to open the semilunar valves against a diastolic pressure of 80 mm. Hg. In the lower portion of the illustration the same concepts are applied to diastolic hypertension (120 mm. Hg of pressure). Consult text for details.

in Fig. 5. A normal sized left ventricle with an end-diastolic volume of 100 c.c. and a diastolic blood pressure of 80 mm. Hg (10.7×10^4 dynes/cm.^{2}) is assumed to contract and eject 75 c.c. of blood while developing a maximal pressure of 120 mm. Hg (16.0×10^4 dynes/cm.^{2}). The time course of change in intraventricular pressure is assumed to represent the time course of change in manifest tension. The tension developed by the wall of the contracting myocardium (T) during early and late systole was derived by use of a parallelogram of forces, the sides of which are determined by the length of the vector representing manifest tension (P) and the radius of the sphere. The same considerations were applied to a dilated heart with an end-diastolic volume of 500 c.c. In the normal sized heart, a change in manifest tension (ventricular pressure) from 10.7×10^4 dynes/cm.^{2} at the end of isometric contraction to 15.5×10^4 dynes/cm.^{2} during rapid ejection to 16.0×10^4 dynes/cm.^{2} at

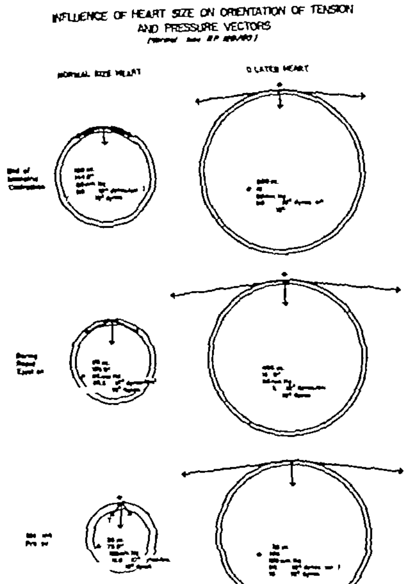


Fig. 5. Influence of change in heart size on the time course of tension (T) and pressure (P) vectors and on hoop angle during systole for a normal and dilated heart. Contractile tension vectors (T) for the normal sized heart necessary to maintain intraventricular pressure are of considerably less magnitude than those for the dilated heart. Because of their orientation they produce a greater resultant force (P) in the normal than in the dilated heart. Consult text.

maximum pressure is associated with a decrease in contractile tension (T). However in the dilated heart a similar change in pressure is associated with an increase in contractile tension. The time course of contractile tension and the change in hoop angle for the normal sized and the dilated heart are shown in Fig. 6. The relatively slight decrease in the magnitude of Θ in the dilated heart as compared to that in the normal sized heart is responsible for the failure of the contractile tension

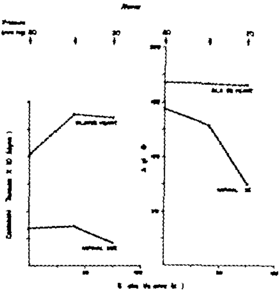


Fig. 4. Influence of change in heart size during systole on contractile tension and hoop angle for a normal sized and dilated heart.

in the dilated heart to decrease during systole.

It is evident that a heart of normal size can develop a greater manifest tension, i.e., a higher intraventricular pressure, for the same contractile force than a dilated heart. Thus regardless of the underlying disease process, dilatation is disadvantageous from the purely geometric or mechanical standpoint. Obviously, impairment of heart muscle by disease would influence the efficiency of myocardial contraction and would add to the problems already created by dilatation alone.

Summary

The purpose of this discussion was to show, on the basis of purely theoretical considerations, that the ability of contractile myocardial tension to raise intraventricular pressure is related to the size (geometry) of the ventricle. Tangentially acting contractile myocardial tension produces a radially acting resultant force (manifest or effective tension) which is equal to intraventricular pressure. In the dilated heart the hoop angle, i.e., the angle between two representative vectors of contractile tension acting tangentially to the ventricular wall, is wide and decreases only slightly during systole. On the other hand, in the normal sized heart the hoop angle is narrow and decreases in magnitude markedly during systole. The effectiveness with which the tangentially acting forces of myocardial contractile tension raise intraventricular pressure depends in part at least upon the magnitude of the hoop angle. The wider the hoop angle the less effective the forces of contractile tension become in raising intraventricular pressure. Therefore, greater contractile tension is necessary to support a given intraventricular pressure for the dilated than for the normal sized heart.

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Effects of muscular activity upon the acute myocarditis of C3H mice infected with Trypanosoma cruzi

*Shia H. Elson, M.D.**
*Walter H. Abelmann, M.D.***
Boston, Mass.

In the care and treatment of patients with myocarditis, rest and limitation of muscular activity are usually recommended, at least during the symptomatic phase of the illness. A relationship is implied between the level of muscular activity and the infectious process or inflammatory response. A search of the literature failed to produce any evidence that such a relationship has ever been established for any myocarditis. The present study was designed to investigate any relationship that might exist between the severity and course of an acute experimental myocarditis and muscular activity.

Acute myocarditis in the C3H mouse due to *Trypanosoma cruzi*, previously studied in this laboratory,[1] was used as the experimental model.

Materials and methods

Design of experiment. The prime purpose of the study was to test the effect of acute infection with *T. cruzi* and of forced exercise, singly and in combination, upon the C3H mouse.

In a previous study, spontaneous activity was found to be decreased in C3H mice with chronic myocarditis and myositis due to *T. cruzi*.[1] Therefore, spontaneous activity was measured also in the present experiment.

Ninety-two mice were divided at random into six approximately equal groups, as indicated in Table I. An additional 30 mice, 15 in Group A and 15 in Group B, were observed for body weight and appearance only as part of a long-term study; they were not included in the pathologic studies.

Mice. The experimental animals were male C3H mice, 4 to 5 weeks of age, obtained from the Jackson Laboratory, Bar Harbor, Maine. The C3H mouse was chosen for its high degree of genetic uniformity, as well as for its known susceptibility to *T. cruzi*.[2] Young mice were used because of their increased susceptibility.[3,4] Female mice were excluded because of the known effect of estrus upon bodily activity.[5] Animals were housed 6 per cage (5 by 8 by 5 inches), kept at a temperature of approximately 22°C. They were fed water and standard Purina rat chow *ad*

From the Thorndike Memorial Laboratory and the Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

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*Work done during the tenure of [illegible] Fellowship of the Massachusetts Heart Association. Present address: Grady Memorial Hospital, Atlanta, Ga.

**Address: Thorndike Memorial Laboratory, Boston City Hospital, Boston, Mass. [illegible]

*Table I. Design of experiment**

Group	Number of animals	Infection	Activity	Swim
A	14	0	0	0
B	15	+	0	0
C	15	0	+	0
D	15	+	+	0
E	15	0	0	+
F	18	+	0	+

*0 = Absent + = Present

libitum. The animals were weighed at weekly intervals.

Origin of T. cruzi. The strain of *T. cruzi* was obtained from Dr. Franklin A. Neva of the Harvard School of Public Health; it had been passed serially in Harvard Swiss mice. The detailed passage history of this strain of *T. cruzi* (Colombian) as well as the clinical and pathologic course of the disease it characteristically produces in C3H mice have been reported previously.[1] After the thirty-first passage in Swiss mice, the parasite was passed once through C3H mice before being used in the present experiment.

Methods of inoculation and parasite counts. Passage of *T. cruzi* was effected by bleeding donor mice from the heart during the acute stage of the infection. An aliquant of heparinized blood was diluted with saline and motile trypanosomes were counted with a hemocytometer. Recipient mice were given inocula of 0.3 ml. intraperitoneally containing 9,000 organisms.

At weekly intervals the degree of parasitemia was estimated semiquantitatively in all inoculated animals.[1] The results were expressed as the average number of trypanosomes per HPF (high power field).

Spontaneous activity. Spontaneous activity, hereafter referred to as "activity," was measured in activity wheels described previously.[1] Activity is expressed in terms of revolutions per minute.

Mice whose activity was to be measured subsequently received two 3 hour acclimatization periods and two 50 minute control runs in the activity wheels before the day of inoculation. After inoculation activity was measured during periods of 50 minutes twice a week for 6 weeks. The duration and frequency of these periods, selected on the basis of previous work,[1] were designed to represent measurements of spontaneous activity rather than forced activity.

Forced exercise. Swimming was the form of forced exercise chosen. Aquaria of glass measuring 18 by 10 by 10 inches were filled with water at 33°C. to a height of 6.5 inches. All animals from one cage—usually 6 mice—swam together in one aquarium. During the week prior to the day of inoculation, mice were placed in the aquaria for increasing periods of acclimatization. After the day of inoculation mice were made to swim for periods of 60 minutes five times per week during 6 consecutive weeks. The swimming mice were watched carefully. When drowning appeared to be imminent, the swimming period was terminated for that animal.

The duration of the swim periods was selected because previous experience indicated an increasing frequency of "going under" and drowning after the first hour of swimming. The frequency of swim periods was selected on the basis of a preliminary experiment in which 9 eight-month-old C3H mice were made to swim to exhaustion—which normally occurred in about 2 hours—five times a week over a period of 2½ weeks. Total swimming time ranged from 10 to 32 hours. Heart

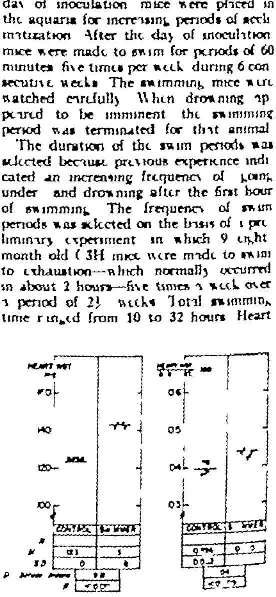


Fig. 1. The effect of exercise upon heart weight tested in 8-month-old C3H mice swimming for 10 to 32 hours distributed over 2½ weeks.

weight was increased significantly by this type of exercise as shown in Fig 1

Pathology The mice were sacrificed with ether on days 49 50 and 51 The body weight at that time was recorded The heart was severed in a standardized manner 2 mm above the origin of the great vessels and was weighed to the nearest 0 2 mg (precision balance*) Portions of the heart lung diaphragm cardioesophageal junction liver spleen colon kidney and skeletal muscle were taken for microscopic study Tissues were fixed in Zenker s acetic solution embedded in paraffin sectioned at 8 μ and stained with hematoxylin and eosin

Approximately five sections per heart were examined The severity of cellular and parasitic infiltration was graded by both authors independently and without knowledge of the identity of the slides Each heart was graded 1+ 2+ or 3+ (mild moderate or severe) for cellular infiltration The number of parasitized cells in one complete section was counted and recorded Aliquots of approximately half of the hearts of each group were weighed and set aside for measurement of dry weight These aliquants were dried in an oven at 90 C for a minimum of 48 hours They were weighed to the nearest 0 01 mg on a Mettler analytical balance Model B 6 dried again and reweighed until weights were stable

Results

The results are presented in Table II

Uninfected and infected controls (*Groups A and B*) There was no significant difference between the appearance of the infected mice and that of the uninfected mice The parasitemia reached a peak on the thirty fifth day and was approaching zero at the termination of the experiment (Fig 2)

The body weight of the infected animals rose rapidly and significantly ($p < 0.001$) above that of the uninfected mice just before the documentation of parasites in the blood on day 14 and then stabilized The final weight was significantly lower ($p < 0.001$) than that of the uninfected animals which continued to gain (Fig 2)

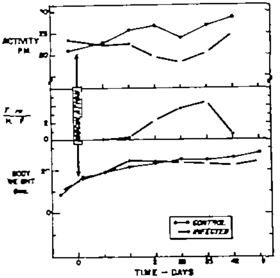


Fig 2 The course of spontaneous activity (*top*) parasitemia (*center*) and body weight (*bottom*) in mice infected with *T cruzi* compared to control Points represent mean values Spontaneous activity of the infected Group D (14 mice) was significantly decreased between day 21 ($p < 0.01$) and day 35 from that of the control Group C (15 mice) Mean level of parasitemia indicated for the 15 infected control mice in Group B Body weight of the infected Groups B and D exceeded that of the control Group A C and E significantly ($p < 0.001$) on day 14 but fell significantly below that of the control groups on day 42 ($p < 0.001$) and day 49

At the end of the seventh week of infection the mean weight of the infected hearts was significantly greater than the mean weight of the control hearts ($p < 0.015$) (Fig 3) even though the body weights of the infected animals were lower (Fig 2) Therefore the heart weight body weight ratios of the infected animals were significantly greater ($p < 0.001$) than those of the uninfected controls (Table II Fig 3)

Gross pathologic examination revealed enlargement of the heart especially of the right atrium and the right ventricle in several infected animals The spleens of all the infected animals were enlarged There was no evident enlargement of esophagus or colon

On microscopic examination there was focal and diffuse mononuclear infiltration of the myocardium associated with patchy necrosis There was some tendency for the infiltrates to involve especially the

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Table II Body weight and heart weight analyzed with respect to infection, activity in drums and swimming

	Activity	Control	Swim	Significance of differences: Activity vs control	Significance of differences: Control vs swim
Body weight (Gm)					
NI*—N	15	29	30		
Mean	24 0	23 5	24 3	N S	<0 1
S D	±1 7	±1 9	±1 5		
I†—N	14	15	14		
Mean	21 9	21 9	19 7	N S	<0 025
S D	±2 1	±2 4	±1 8		
Significance of difference between NI and I	<0 05	<0 01	<0 001		
Heart weight (mg)					
NI—N	15	14	15		
Mean	95 3	91 3	99 9	<0 4	<0 025
S D	±7 0	±10 1	±6 4		
I†—N	14	15	14		
Mean	98 3	100 9	99 4	N S	N S
S D	±11 4	±11 5	±9 8		
Significance of difference between NI and I	N S	<0 05	N S		
Heart wt Body wt ×100					
NI —N	15	14	15		
Mean	0 399	0 385	0 416	<0 2	<0 005
S D	±0 024	±0 026	±0 023		
I† —N	14	15	14		
Mean	0 485	0 461	0 506	<0 2	<0 005
S D	±0 057	±0 078	±0 045		
Significance of difference between NI and I	<0 001	<0 001	<0 001		

*Not infected
†Infected.
Early deaths have been excluded.

subepicardial muscle layer Scattered leishmanial forms of *T cruzi* were seen Skeletal muscle howed ... ular lesions with focal and diffuse ... nuclear in filtration and occasion ıl ... llular or ganisms

Uninfected and infect ... groups (Groups C and D) The ı ... tivity (Group C) and infected ... ıp D) groups did not differ fro ... cted control (Group A) and ... d (Group B) groups with

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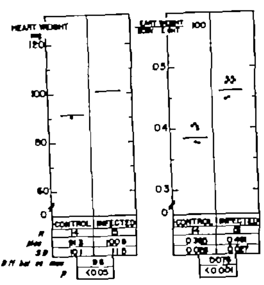


Fig 3 The effect of the infection upon heart weight Comparison of Group A (*open dots*) and Group B (*solid dots*)

from the uninfected controls (Group A) in only the heart weight Body weights were essentially the same but the hearts of the swimmers were significantly heavier ($p < 0.025$) as indicated in Table II

Infected swimmers (Group F) In appearance and trypanosome counts the infected swimmers did not differ from the other groups Four infected swimmers died during the course of the experiment 3 of these during swimming One of the latter died with pulmonary edema the only such case *in this experiment* The other 2 succumbed to either drowning or cardiac arrhythmia There was only one other early death in the infected activity Group D

The body weight curve closely paralleled the curve of the infected controls The final mean body weight of the infected swimmers was 19 7 Gm as compared to 21 9 Gm for the infected control group (Table II Fig 2) This difference was thought to be spurious inasmuch as it was found that at the beginning of the experiment the mean body weight of the infected control group significantly exceeded that of the infected swimmers by 2 4 Gm Fortunately there were no significant differences between the initial weights of other groups in this experiment In order to permit comparison of the heart weights

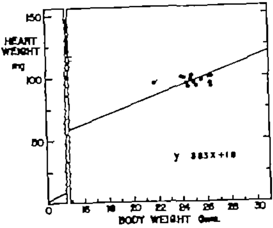


Fig 4 Regression of heart weight upon body weight in 29 C3H mice which were 10 to 12 weeks old Note that the regression line reaches the Y axis close to 0 validating the use of the heart weight/body weight ratios

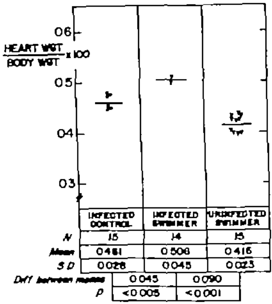


Fig 5 The additive effect of swimming and infection combined (*center*) upon the heart weight/body weight ratio compared to the effect of infection alone (*left*) and that of swimming alone (*right*)

of the infected swimmer group with the heart weights of other groups it was necessary to take body weight into consideration

Data derived from 29 control C3H mice ranging from 18 9 to 29 6 Gm in weight were used to determine the regression of heart weight upon body weight The data fitted a straight line (Fig 4) in agreement with previous data for rats and guinea pigs by Beznak[4] and Van Liere respec

tively. The normal regression line for the present experiment was Y = 3.83x + 1.8. These control data were used to fit the formula Y = ax^b, where Y = heart weight, a = constant, x = body weight, and b = constant, as given by Huxley.[4] The exponential constant b was found to equal 0.986 and did not differ significantly from 1. It can be seen from the formula that when b = 1, the ratio Y/x is equal to a constant, a. Hence, the use of the heart weight/body weight ratios in the comparison of groups of animals in the present study was valid.

In a comparison of heart weight to body weight ratios, the hearts of the infected swimmers were found to be significantly heavier than those of the infected controls and of the uninfected swimmers (Table II, Fig. 5).

The infected swimmers' hearts were generally larger in proportion to the size of the mouse than were the hearts of any other group. Microscopically, the cellular



Fig. 6. Section of myocardium from a mouse of Group B (infected swimmer) 30 days after inoculation with *T. cruzi*. Note moderate cellular infiltration. Hematoxylin and eosin stain. ×300.



Fig. 7. Section of myocardium from a mouse of Group I (infected swimmer) 30 days after inoculation. Note extensive infiltration and necrosis as well as two foci of leishmanial forms of *T. cruzi*. Hematoxylin and eosin. ×200.

infiltration in the swimming group was more diffuse and the necrosis more severe than that in the control group (Figs. 6 and 7). This was confirmed statistically by blind study. The average infiltration for the infected controls was 2.2 + (N = 13), whereas the average infiltration for the *infected swimmers was 2.7 +* (N = 17); the difference between these means was significant ($p < 0.01$). The average number of infected cells per section of the infected controls was 0.6, compared to 1.3 for the infected swimmers. This difference was not quite significant ($p < 0.1$).

The mean dry heart weight, expressed as per cent of wet heart weight, for the entire sampled infected group of 18 mice was 20.5 per cent, with a standard deviation of 1.7 per cent. The mean of the uninfected group of 18 mice was not significantly different at 21.3 per cent, S.D. 1.3. Six animals of each of these two groups of 18 were in the activity group and 6

were in the swimming group their dry weight to wet weight ratios were not significantly different

Discussion

It has been well established that physical exercise may result in cardiac hypertrophy in the rat[4,12] and in the guinea pig[13,14] The present study confirms this for the mouse and presents a simple and effective method of producing cardiac hypertrophy by swimming

There is no agreement as to the pathogenesis of the myocardiopathy associated with *T cruzi* mechanical and toxic effects of the parasite as well as inflammatory allergic responses on the part of the host have been considered Yet in the acute stage with which the present study deals the picture in the myocardium is that of an acute inflammatory process in the presence of leishmanial forms of the parasite and may well be called *acute Chagasic myocarditis* The experiments reported here establish that this form of acute myocarditis in the mouse is associated with a significant increase in heart weight Ratios of dry weight to wet weight indicate that the observed increases in heart weight are not due to edema Although the increase in heart weight may in part be accounted for by the parasitic and cellular infiltrates it should probably be attributed primarily to cardiac hypertrophy

This may represent the first demonstration of cardiac hypertrophy resulting from an acute experimental myocarditis We have been unable to find any report in the literature of proof of such an association nor is acute myocarditis listed among the causes of cardiac hypertrophy in current texts of pathology or cardiology nor in a recent comprehensive review[17] In a recent study in this laboratory the hearts of mice inoculated with Coxsackie A 9 virus were significantly heavier within 2 weeks after infection than those of control animals[18] however water content was not measured Further work with this infection is in progress

Combination of infection with *T cruzi* and forced exercise by swimming resulted in a degree of cardiac hypertrophy significantly greater than that produced by either factor alone The effect of the combination of factors was at least additive if not synergistic The results of the combination of two other agents known to produce cardiac hypertrophy have been reported by Norman and McBroom[19] The production in rats of anemia with phenylhydrazine after the induction of hypertension by unilateral nephrectomy and ligation of the remaining kidney resulted in a degree of cardiac hypertrophy greater than that produced by either method alone although the effect was less than additive In the present study the myocarditis was more severe in mice which also swam as indicated both by the excess mortality and by the histopathology To the authors knowledge this represents the first definite evidence that forced exercise may aggravate an acute myocarditis

In view of the demonstrated relationship between muscular activity and the course of acute myocarditis it is of interest that the spontaneous activity of mice with acute myocarditis due to *T cruzi* was found to be reduced Although this may be considered to be an adaptive response it cannot necessarily be attributed to the changes in the cardiovascular system inasmuch as these were accompanied by inflammatory changes in skeletal muscles Reduction of spontaneous activity during the chronic phase of experimental myocardiopathy associated with *T cruzi* has previously been observed in this laboratory[1]

The usefulness of experimental *T cruzi* infections as a model of myocarditis signaled in a previous communication has been confirmed

Summary

An acute myocarditis was produced in 48 C3H mice by infection with *Trypanosoma cruzi* (Colombian) Spontaneous activity was measured in activity drums and the effects of forced muscular exercise in the form of swimming were studied Fifty days after inoculation the infected as well as the 44 control animals were sacrificed

Spontaneous activity decreased as parasitemia increased and increased again as parasitemia subsided

The ratio of heart weight to body weight was increased significantly by swimming

alone and also by infection alone The combination of both factors resulted in a significantly greater increase in the heart weight body weight ratio than did either alone The ratio of dry heart weight to wet heart weight was not affected by either factor

Swimming was associated with a greater mortality with more severe and more dif fuse cellular infiltration and with a greater number of parasites in the myocardium

The authors are grateful to Dr Malcom Turner and Dr Louis Homer of Emory University for their assistance in the validation of the use of heart weight/body weight ratios and to Miss Elaine V *Jeannotte for technical assistance throughout this* study

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The effects of angiotensin on the circulation and myocardial metabolism of dogs with experimentally produced myocardial infarction

*Jose Ribeilima, M.D.**
Grand Rapids, Mich.

Angiotensin has been used in the treatment of various shock states[1-4] since it quickly raises systemic arterial pressure. A positive inotropic effect[4,5] without significant change in cardiac output[6] has also been attributed to angiotensin. On the other hand, a decrease in cardiac output and an increase in left atrial and pulmonary arterial pressures have been observed in dogs and normal human subjects.[9,10,11] On the basis of these findings and limited clinical experience, the use of angiotensin has been both recommended and cautioned against[1,12] in the treatment of hypotension complicating myocardial infarction.

Since the hemodynamic changes described in patients with myocardial infarction[13,1] are similar to those resulting from experimental myocardial infarction in dogs,[15-17] a detailed study of the effects of angiotensin in the latter condition may have clinical implications. This paper discusses the effects of angiotensin on the circulation and myocardial metabolism of dogs with experimentally produced myocardial infarction.

Materials and methods

The experiments were carried out on 20 mongrel dogs which weighed 18 kilograms or more. Pentobarbital (25 mg. per kilogram of body weight) was given intravenously as anesthetic. Right and left atrial and ventricular, pulmonary arterial, and aortic pressures were obtained through catheters introduced via the left jugular vein, carotid artery, and right brachial artery and vein. Cardiac output was calculated from the dye-dilution curve.[8] In the closed-chest animal, the circumflex coronary artery was then catheterized under fluoroscopic control, and steel ball bearings that measured 1.1 mm. in diameter were injected into the intubated coronary artery, as previously described.[17] Three ball bearings per kilogram of weight were used. The catheter was then withdrawn into the aorta. One hour after embolization, arterial and coronary sinus blood was simultaneously drawn for determination of coronary blood flow by the N_2O method, O_2 content,[1] and concentrations of glucose, lactate,[19] pyruvate,[21] and free fatty acids.[22] Cardiac output, right and left atrial and ventricular, pulmonary arterial, and aortic pressures were again obtained. These observations served as controls. A solution of angiotensin (10 gamma per milliliter) was then started intravenously and in

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*Associate Professor of Medicine, Wayne State University, Detroit, Mich., and Director of Cardiac Laboratory, Blodgett Memorial Hospital, Grand Rapids, Mich.



Fig. 1 Coronary arteriogram obtained before and after embolization of the circumflex coronary artery

fused at a rate fast enough to raise and maintain the aortic pressure at the pre infarction level. One half hour after angiotensin had been started all the previous determinations were repeated. An average of 200 gamma of angiotensin was given to each dog over one half hour. In 10 experiments these same determinations were made at identical time intervals without infusion of angiotensin.

Results

The degree of coronary vascular obstruction produced by the emboli is demonstrated in Fig. 1. The changes observed in circulation and myocardial metabolism after production of myocardial infarction by the method described have been published previously.[8] Hemodynamically a significant decrease in the aortic and pulmonary arterial pressures, cardiac output and coronary blood flow were observed 1 hour after the embolization of the coronary arteries (Table I). Metabolically there was a significant increase in the arterial level of lactate and pyruvate and a higher myocardial extraction of oxygen (Table I). No significant changes in the myocardial extraction of glucose, lactate, pyruvate and free fatty acids were observed.[4] In the present study the determinations obtained in 10 dogs 1 hour after the production of myocardial infarction served as controls for comparison with the results observed during the infusion of angiotensin. In 10 control experiments in which no angiotensin was given there was no significant difference between the hemodynamic and metabolic findings obtained at 1 hour and those obtained at 1½ hours after the production of myocardial infarction; this was in contrast to those experiments in which angiotensin was given.

The hemodynamic changes observed during the infusion of angiotensin are summarized in Table II. There was no significant change in the heart rate and coronary blood flow. The mean aortic, left atrial and pulmonary arterial pressures as well as the peripheral resistance were consistently raised. The cardiac output decreased in all determinations. The metabolic effects of angiotensin are presented in Table III. The arterial levels of lactate and pyruvate and the myocardial extraction of lactate increased significantly. The myocardial extraction of oxygen increased in 6 out of 8 determinations. The myocardial extraction of glucose, pyruvate and free fatty acids did not change significantly (Table III).

Discussion

Perfusion of the heart and body with oxygenated blood is the main objective in the treatment of cardiogenic shock. An increase in aortic pressure is only one means of accomplishing this. It is desirable

Table I. Significant hemodynamic and metabolic changes observed in 20 dogs 1 hour after the production of myocardial infarction

	Before myocardial infarction	*After myocardial infarction*	*p Value*
Mean aortic pressure (mm. Hg)	123	99	< 001
Mean pulmonary arterial pressure (mm. Hg)	16	13	< 05
Cardiac output (L./min.)	3.13	2.13	< 001
Coronary blood flow (c.c./100 Gm. LV/min.)	104	66	< 005
Arterial–coronary sinus O_2 content (vol. %)	14.10	15.10	< 05
Arterial lactate (mg. %)	9.56	13.84	< 05
Arterial pyruvate (mg. %)	337	470	< 05

Results obtained from previous series of experiments.

Table II. Effect of angiotensin in 10 dogs with myocardial infarction

	Before angiotensin	*During angiotensin*	*p Value*
Rate (beats/min.)	153	161	> 25
Cardiac output (L./min.)	2.3	1.81	< 0
Mean aortic pressure (mm. Hg)	112	142	< 001
Total peripheral resistance (units)	43.8	74	< 05
Coronary blood flow (c.c./100 Gm. LV/min.)	92.8	87.4	> 60
Left atrial pressure (mm. Hg)	7	14	< 005
Pulmonary arterial pressure (mm. Hg)	[illegible]	17	< 10

Table III. Effect of angiotensin in 10 dogs with myocardial infarction

	Before angiotensin	*During angiotensin*	*p Value*
Arterial–coronary sinus O_2 (vol. %)	15.9	17.29	< 70
Free fatty acid			
Arterial	831	877	> 50
Arterial–coronary sinus	179	187	> 0
Glucose (mg. %)			
Arterial	78.33	75.24	> 60
Arterial–coronary sinus	11.4	10.71	> 50
Lactate (mg. %)			
Arterial	14.94	22.13	< 05
Arterial–coronary sinus	4.33	9.50	< 10
Pyruvate (mg. %)			
Arterial	34	726	< 0 5
Arterial–coronary sinus	061	044	> 10

that the increase in pressure be mainly the result of a higher cardiac output In the present series of experiments aortic pressure could easily be raised by angiotensin but a lower cardiac output was also consistently produced thus indicating that the increase in aortic pressure was due only to a higher peripheral resistance The increased contractility of the myocardium if it did occur was not enough to compensate for the increased resistance to left ventricular ejection resulting in a lower cardiac output and higher left ventricular end-diastolic left atrial and pulmonary arterial pressures

No significant change in coronary blood flow was produced by the administration of angiotensin An increase in the myocardial extraction of oxygen occurred in 6 out of 8 determinations but was not statistically significant ($p > 10$) Similar findings have also been reported during the infusion of angiotensin in normal human subjects[1]

The arterial levels of lactate and pyruvate which were already elevated after myocardial infarction rose still further after the infusion of angiotensin It is tempting to speculate that increased glycolysis secondary to a decreased cardiac output had occurred No evidence of myocardial glycolysis was observed during the administration of angiotensin actually a significant increase in the myocardial extraction of lactate was observed probably due to the higher arterial concentration of lactate[22]

The increase in the arterial level of lactate the decrease in the already low cardiac output and the increase in left ventricular end-diastolic left atrial and pulmonary arterial pressures caused by the infusion of angiotensin are all undesirable changes when one is treating the severe hypotension that frequently develops in patients with acute myocardial infarction The possibility that patients will react differently cannot be disregarded but Ross and Braunwald[34] recently reported a deterioration of the left ventricular function curves in patients with myocardial disease in whom there was increased resistance to left ventricular ejection after infusion of angiotensin[35] In view of these experimental observations the efficacy of angiotensin in the treatment of cardiogenic shock in man appears doubtful

Summary

Synthetic angiotensin was used to raise the aortic pressure to preinfarction level in dogs with recently produced myocardial infarction The increase in aortic pressure was consistently accompanied by a decrease in cardiac output and elevation of the left ventricular end diastolic left atrial and pulmonary arterial pressures An increase in the arterial level of lactate and and pyruvate was also observed The only significant change in myocardial utilization of substrates was an increase in the myocardial extraction of lactate In view of these findings the usefulness of angiotensin *for the treatment of cardiogenic* shock is questioned

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Electrocardiographic findings associated with experimental arborization block in dogs

*Thomas B Wall Jr M D Ph D**
*Raymond D Pruitt M D M S (Med)***
Houston Tex

The location and extent of septal lesions which will produce identifiable conduction defects concern both the physiologist and the clinician For the physiologist this knowledge would permit better definition of the functional individuality of specific divisions of the main bundle branches For the clinician such information would render more likely or less likely the recognition of occult septal infarcts on the basis of changes in QRS form or mean electrical axis

One type of septal injury transection of rami of the left bundle branch distal to the point of arborization of the main bundle is illustrated by the experiments reported herein

Methods

All experiments were performed on adult mongrel dogs each weighing about 15 kilograms Under pentobarbital anesthesia the chest was opened via a midline sternal incision and the pericardium was fashioned into a sling supporting the exposed heart In order to guide a No 1 black silk ligature into proper position a copper wire electrode was fashioned as illustrated in Fig 1 Insulation remained intact except at the upper lead connection at the groove for the ligature along the shaft and at the tip from which signals indicated continuously whether the electrode traversed septum or cavity This electrode was first passed through the septum (*broken line*) and threaded spirally far enough to expose the groove at the exit wound To this groove one end of the ligature was securely fastened Pulling back on the wire electrode then withdrew the end of the ligature along the electrode path to the entrance wound By the same method the other end of the ligature was positioned between identical exit and entrance wounds but across a portion of the left ventricular cavity (*solid line*) In general for transecting anterior fibers the electrode was passed from an anterolateral basal point to an apical point for posterior fibers from an apical point to a posterobasal point and for high septal lacerations including total interruption of the left bundle branch system from an anterolateral basal point to a posterobasal point Next by drawing the free ends of the ligature back and forth all intervening tissue was severed A guard made from a large hypodermic needle minimized laceration of the epicardial surface at the entrance wound ventrally rendering surgical closure of that wound usually unnecessary

Conventional unipolar and bipolar extremital leads and a right and left chest lead were recorded before and after each procedure Additional leads commonly were made either from precordial points or from the esophagus posteriorly and all

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*Assistant Professor Department of Internal Medicine Baylor University College of Medicine and Veterans Administration Hospital [illegible] Houston Tex
**Professor and Chairman Department of Internal Medicine Baylor University College of Medicine Houston Tex

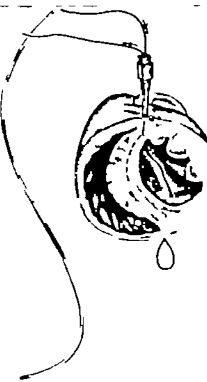


Fig 1 Left Drawing of the helix shaped electrode which was constructed of AWG No 14 enameled copper wire and beveled t the tip The annular groov facilitates attachment of the ligature Right Drawing of a heart section to illustrate the path of the ligature before sewing (See text for further details)

later experiments included also multiple direct epicardial unipolar leads utilizing a saline soaked cotton tipped soft electrode

Finally the extent of the lesion was determined by examination of the interior of the left ventricle

Results

In the course of 21 earlier experiments [1] many types of septal lacerations were obtained severing anterior fibers middle fibers posterior fibers and various combinations of these Except for 4 instances of complete left bundle branch block after total interruption of all left bundle branch fibers (illustrated in Fig ?) electrocardiographic alterations were limited More refined methods were needed for displaying the effects of less than total transections of the left bundle branch hence additional experiments herein reported included the recording of potentials directly from the epicardium From a total of 53 such experiments 11 resulted in unsatisfactory lesions and were therefore excluded Of the other 42 (32 anterior and 10 posterior lacerations) 4 have been selected for presentation as most representative These include (I) an anterior septal laceration showing minimal axis shift in conventional leads (II) an anterior septal laceration showing the greatest shift in axis encountered in this series of experiments (III) electrocardiographic changes resulting from a typical posterior septal laceration and (IV) one of five experiments in which an anterior septal lacerations was allowed to heal before a second laceration was produced posteriorly

I Anterior septal laceration attended by minimal axis shift Fig 3 includes a photograph of the interior of the left ventricle in which can be identified remnants of fibers of the anterior false cord which curl back upon themselves just proximal to the laceration Remnants of these same fibers distal to the lesion are almost hidden by the bulge of the anterior papillary muscle Contrast these structures with the uninjured posterior fibers including the posterior false cord which leaves the septum to run free in the left ventricular cavity and attach to the posterior papillary muscle at the right of the picture

In the lower portion of the figure are electrocardiograms recorded before and after production of this lesion Neither QRS axis nor QRS duration appeared to be appreciably altered Scrutiny of the tracings reveals only minute changes of form (small Q in Lead I after laceration with a loss of Q and development of nearly imperceptible terminal S in Leads III and aVF) Although the degree of axis shift in this experiment was minimal for a septal laceration which severed so high a proportion of the anterior division rami this and slightly greater shifts were the usual result of anterior septal lacerations not the more marked alterations presented in Figs 5 and 10

More striking electrocardiographic effects occurred in leads in contact with the epicardium of the left ventricle The changes which developed here are of a kind and degree encountered in similar leads from other experiments in which a comparable

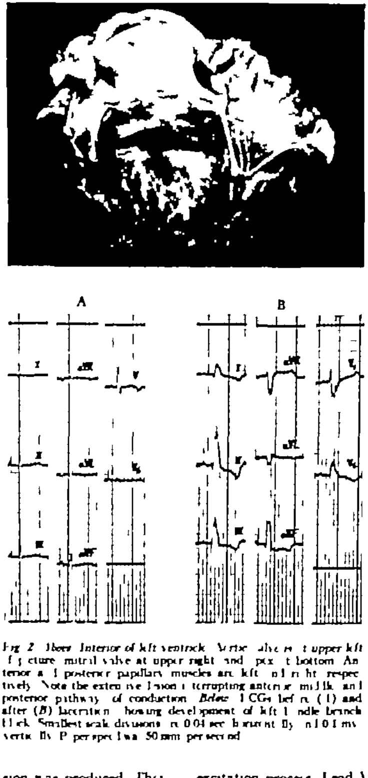
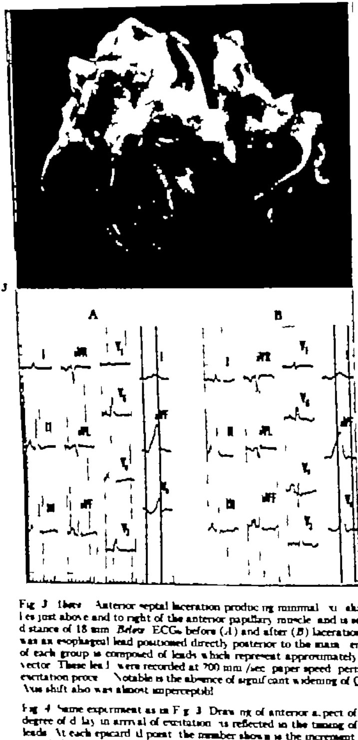


Fig 2 Above Interior of left ventricle. Aortic valve is at upper left of picture, mitral valve at upper right and apex at bottom. Anterior and posterior papillary muscles are left and right respectively. Note the extensive lesion interrupting anterior, middle and posterior pathways of conduction. *Below* ECGs before (A) and after (*B*) laceration showing development of left bundle branch block. Smallest scale divisions are 0.04 sec horizontally and 0.1 mv vertically. Paper speed was 50 mm per second.

anterior septal lesion was produced. They appear in QRS complexes derived from epicardial regions overlying those portions of subendocardium distal to the laceration. These changes summarized in Table I are the following: (a) Delay in arrival of the excitation process. Lead V in Fig. 4 was derived from a point at which timing of the intrinsic deflection increased from 30 to 54 msec, indicated on the figure as *24*, which number defines in milliseconds the delay imposed by septal laceration. Simi

3



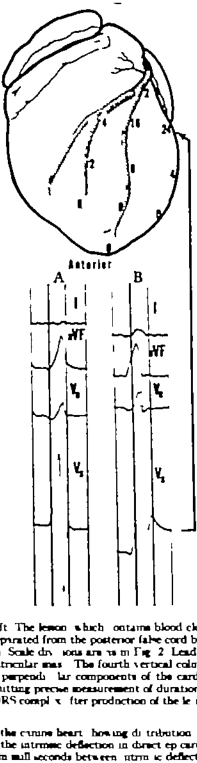


Fig 4

Fig 3 *Above* Anterior septal laceration producing minimal axis shift The lesion which contains blood clots lies just above and to right of the anterior papillary muscle and is separated from the posterior false cord by a distance of 18 mm *Below* ECGs before (*A*) and after (*B*) laceration Scale divisions are as in Fig 2 Lead V was an esophageal lead positioned directly posterior to the main ventricular mass The fourth vertical column of each group is composed of leads which represent approximately perpendicular components of the cardiac vector These leads were recorded at 200 mm /sec paper speed permitting precise measurement of duration of excitation process Notable is the absence of significant widening of QRS complex after production of the lesion Axis shift also was almost imperceptible

Fig 4 Same experiment as in Fig 3 Drawing of anterior aspect of the canine heart showing distribution and degree of delay in arrival of excitation as reflected in the timing of the intrinsic deflection in direct epicardial leads At each epicardial point the number shown is the increment in milliseconds between intrinsic deflection time before laceration and that after laceration A representative complex from a direct epicardial lead (V) over the most delayed point recorded (*indicated by arrow*) is presented in the lower half of the figure In *A* before production of the lesion intrinsic deflection time was 30 msec R and S deflections were about equal in size and no Q wave was present In *B* after production of the lesion intrinsic deflection time had increased to 54 msec (delay of 24 msec —indicated by the number 24 on the drawing) R had become larger and S smaller and a Q wave had appeared Paper speed was 200 mm /sec

larly; other numbers designate increments of intrinsic deflection time found at each respective point. (b) Increase in R/S ratio. (c) Appearance of a Q deflection or widening and/or deepening of a pre-existing Q.

The consistency with which these electrocardiographic changes appeared was sufficient to justify their subsequent use in delineating the boundaries of the epicardial area of involvement and in predicting approximately the extent of the septal laceration prior to completion of an experiment.

II. Anterior septal laceration attended by greatest axis shift. Figs. 5 and 6 were derived from an experiment in which an anterior septal lesion caused a shift in mean QRS axis from about +70 to about +50 degrees. Not only was this lesion longer than the lesion in the experiment just reported, but also its posterior component involved septal tissue close to the fibers of the posterior false cord. The increase here noted in the depth of S in Leads III and aVF, with the corresponding increase in the height of R in Lead aVL, were characteristic of all large subtotal lesions produced. Such lacerations would interfere with collateral conduction which otherwise might have followed a septal pathway to the apex and thence to the anterolateral free wall.

Comparison of Fig. 6 with Fig. 4 discloses little difference in the maximal degree of delay to the blocked region, but a major difference in the size of the region in which significant delays developed. Maximal delay of about 20 msec. was encountered in the majority of experiments in which anterior septal conduction fibers were transected.

III. Posterior septal laceration. Figs. 7 and 8 are representative of anatomic and electrocardiographic findings associated with the interruption of posterior fibers of the left bundle branch by septal laceration. Both proximal and distal remnants of the posterior false cord can be identified at the edges of the deep open wound. Anterior fibers, to the left in the picture, appear to be unharmed.

Electrocardiographic alterations included nearly complete loss of terminal S in Leads II, III, and aVF, with reciprocal diminution of late R in Leads aVR and aVL.

Table I. Changes in epicardial leads from a region of arborization block

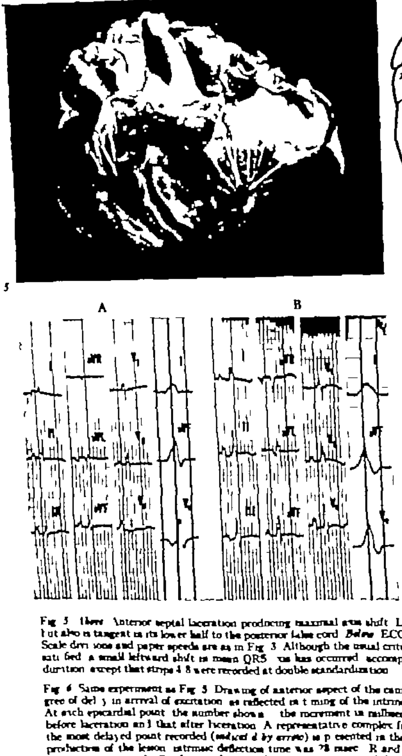
Characteristic observed	*Anterior lesion*	*Posterior lesion*
Number of experiments	32	10
Intrinsic delay ≥ 6 msec	31	6
Increased R/S ratio	32	6
Q wave development	14	6

Any increase in duration of QRS was equivocal.

Fig. 8 illustrates changes in timing of the intrinsic deflection of QRS in a direct lead from a mid-posterior epicardial point. The deflection occurred at 35 msec. in the control tracing and at 52 msec. after severance of the posterior fibers of the left bundle branch, an imposed delay of 17 msec. This delay was less than that encountered at certain anterior epicardial points after an anterior septal lesion. However, the posterior epicardial points were excited later than anterior points in control records, thus suggesting that the lesser delay after a posterior lesion resulted from a more effective detour via the physiologically earlier excited subendocardial pathways in the anterior septum. An increase in the height of R posteriorly was accompanied by reciprocal deepening of S at anterolateral points on the epicardium. No Q wave appeared, but the R wave developed an initial slow rise component.

IV. Chronic anterior plus acute posterior lesions. Figs. 9 through 12 illustrate a more involved experiment which permitted appraisal of the electrocardiographic consequences of closing the chest, of healing of the initial septal laceration, and of combining a chronic anterior with an acute posterior septal laceration.

The left ventricular septum as shown in Fig. 9 contains two lesions. On the left is a well-healed, comma-shaped, 53-day-old anterior septal scar into which is bound the proximal end of the distal remnant of the anterior false cord. On the right, and somewhat apically, is the gaping, fresh laceration interrupting posterior septal fibers of the left bundle branch. Electrocardiographic data suggest that all apically



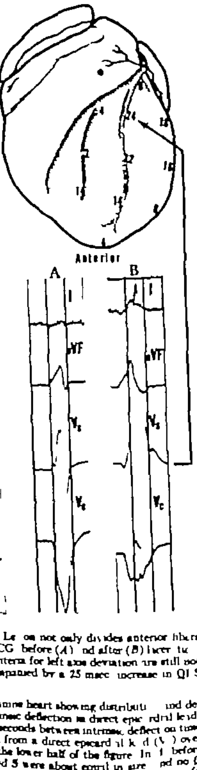
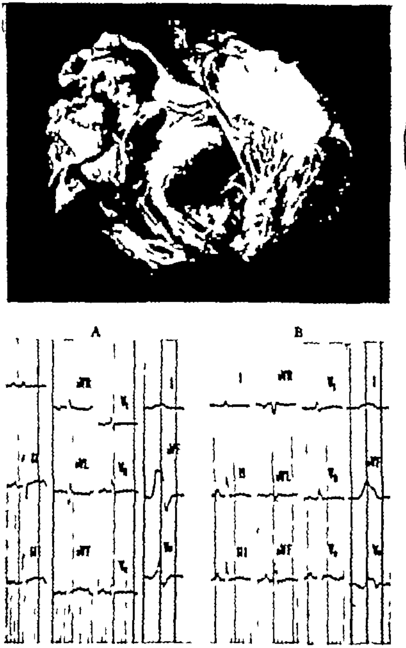


Fig 5 Above Anterior septal laceration producing maximal axis shift Le on not only divides anterior fibers but also is tangent in its lower half to the posterior false cord *Below* ECG before (*A*) nd after (*B*) lacer tio Scale divi ions and paper speeds are as in Fig 3 Although the usual criteria for left axis deviation are still not satisfied a small leftward shift in mean QRS xis has occurred accompanied by a 25 msec increase in QRS duration except that strips 4 8 were recorded at double standardization

Fig 6 Same experiment as Fig 5 Drawing of anterior aspect of the canine heart showing distributi nd degree of del y in arrival of excitation as reflected in t ming of the intrinsic deflection in direct epic rdial le d At each epicardial point the number show n the increment in milliseconds between intrinsic deflect on time before laceration an l that after laceration A representative complex from a direct epicard al le d (V) over the most delayed point recorded (*indicat d by arrow*) is p esented in the lower half of the figure In A before production of the lesion intrinsic deflection time was 78 msec R and S were about equal in size nd no *Q* wave was present In *B* after production of the lesion intrins c deflection time had increased to 32 msec (a delay of 4 msec —ind cated by the number *24* on the drawing) R had become larger and S sm ller and a Q wa e had appeared Leads included V from the cavity of the left entricle Paper speed was 200 mm per second



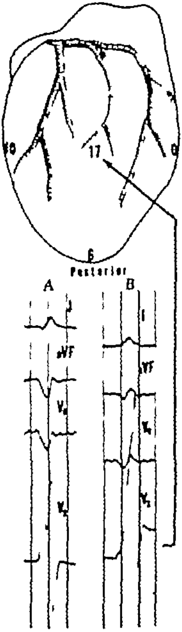


Fig. 7. *Above,* Posterior septal [illegible] Intact fibers of the anterior [illegible] can be seen [illegible] between [illegible] at the left of the photograph. *Below,* ECG before (A) and after (B) [illegible]. Scale [illegible] and paper speed [illegible] Fig. 3. A definite shift occurred in the [illegible] terminal QRS [illegible] to an [illegible] direction although mean QRS [illegible] remained within [illegible]. [illegible] QRS duration was equivocal.

Fig. 8. Same experiment as Fig. 7. Drawing of posterior [illegible] of the [illegible] heart showing degree of delay in arrival of excitation [illegible] reflected in timing of the intrinsic deflection in [illegible] epicardial lead. At each epicardial point, the number shown is the increment in milliseconds between intrinsic deflection time before [illegible] and that after [illegible]. A representative complex from a direct epicardial lead (V) over a [illegible] posterior point (indicated by arrow) is presented in the lower half of the figure. In A, before production of the lesion, intrinsic deflection time was 35 msec. R was only slightly larger than S and no Q was seen [illegible] present. In B, after production of the lesion, intrinsic deflection time had increased to 52 msec. ([illegible] delay of 17 msec. [illegible] by the number 17 on the drawing). R had become larger and S smaller and an [illegible] delta-like segment had appeared on the upstroke of the R deflection. Paper speed was 200 mm. [illegible]



Fig 9 Interior of left ventricle showing terior and posterior laceration The anterior scar extend from the tip of the papillary muscle mediall to the ttachment of the di tal remnant of the anterior false cord thence inferiorly to a mid-septal point The fresh posterior laceration pared high posterior fibers transected main posterior fibers including the trunk of the posterior fal e cord and overlapped the apical end of the anterior lesion Note the single strand of fibers which runs from the posterior septum to the tip of the posterior papillary muscle Electrocardiographic evidence suggested that this trand carried excitation into the left entricular free wall and prevented development of left bundle branch block

directed subendocardial conduction path ways were interrupted by these two lacera tions However high posterior fibers re mained intact at the posterobasal end of the posterior (*right hand*) lesion The combined effect of these lesions was there fore to isolate the anteroseptal antero lateral and apical portions of left ven tricular myocardium from direct pathways of excitation

Comparison of column *A* in Fig 10 with column 1 in Fig 11 discloses a loss of volt age in ventricular complexes when the chest was opened the electrical axis remained unchanged Anterior septal laceration (col umn *B* of Fig 11) produced a slight in crease in the depth of S in Leads II III and aVF and a slight increase in terminal R in Lead aVL These changes were more evident after the chest had been closed as seen in tracings recorded the following day (column *B* of Fig 10) During the succeed ing 52 days no further changes occurred (column *C* of Fig 10) Opening the chest preparatory to the production of a pos terior septal laceration (column *C* of Fig 11) again resulted in a loss of QRS voltages in all leads and a decrease in R of Leads I and aVL Posterior septal laceration (col umn *D* of Fig 11) almost completely rever ed the changes resulting from the now healed anterior septal lesion The sequence of enlarged complexes at the bottom of Fig 11 discloses preferentially the shift of electrical axis which attended the production of the anterior septal lacera tion and reversal of that shift after the production of the posterior septal lacera tion The Q wave in the control tracing never reappeared and QRS remained slightly prolonged

In the epicardial leads (V) reproduced in Fig 12 the major electrocardiographic consequences of anterior septal laceration

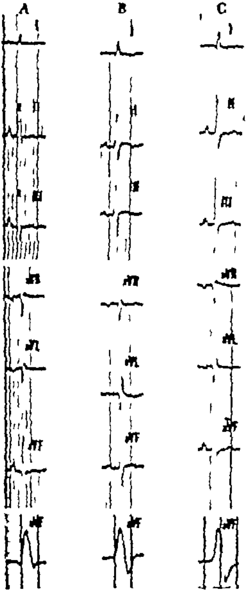


Fig. 10

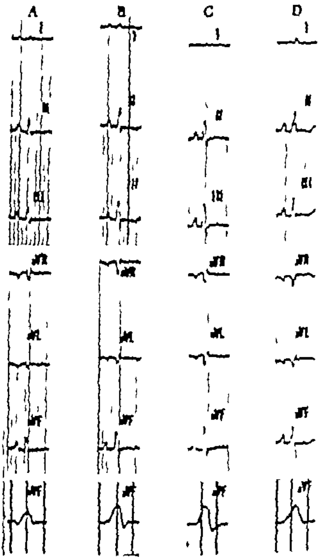


Fig. 11

Fig. 10. [illegible] (A) before [illegible] (B) [illegible] after [illegible] and (C) [illegible] after [illegible] Lead V1 taken at [illegible] mm/sec [illegible] QRS [illegible] the [illegible] position.

Fig. 11. [illegible] (A) before [illegible] (B) [illegible] after [illegible] (C) before [illegible] and (D) immediately after [illegible] each column. Lead aV[illegible] taken at 200 mm/sec [illegible] QRS [illegible] recorded with the [illegible] in the supine position.

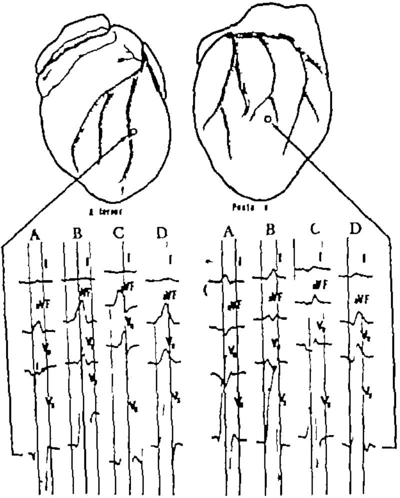


Fig 17 In each column the leads are from top to bottom I aVF V (esophageal) and V (soft electrode on epicardium) Placement of each epicardial electrode is indicated by the small circle on the anterior and posterior drawing corresponding to left and right groups of tracings respectively In each group specific columns are (A) before anterior laceration (B) after anterior laceration (C) before posterior laceration and (D) after posterior laceration For additional detail see text Paper speed was 200 mm / sec

were a delay in timing of the intrinsic deflection and an increase in the R/S ratio in anterior leads represented by columns *A* and *B* in the left half of the illustration Similar consequences of posterior septal laceration were observed in posterior leads represented by columns *C* and *D* in the right half of the illustration Columns *A* and *B* on the right and *C* and *D* on the left demonstrate minor reciprocal changes in leads opposite to primarily delivered regions after anterior and posterior lacerations respectively

Discussion

Arborization block as originally defined by Oppenheimer and Rothschild was characterized by the following features (1) QRS duration of more than 0 1 second (2) notching of R wave (3) usually low voltage of QRS (4) absence of characteristic T wave changes At necropsy on patients so affected a diffuse sclerosis especially in the region of the left septal endocardium was commonly observed Subsequently controversy arose in regard to the effect of a smaller more discrete

lesion placed precisely in a major subdivision of the left branch of the bundle of His. Wilson and Herrmann[4] on reviewing the earlier work of Lewis concluded that only minor electrocardiographic alterations would be produced by such an injury. After the introduction of precordial leads Wilson and associates redefined the criteria for arborization block; they acknowledged the existence of postinfarction conduction defects but ascribed them, as had Oppenheimer and Rothschild, to diffuse sclerosis rather than to focal transection of conduction tissue alone. This position was supported by First, Bayley, and Bedford,[6] who designated the condition peri-infarction block. More recently, Grant and Murray,[8] Grant and Dodge,[7] and Grant[1] have proposed that a specific focal disturbance in peripheral left ventricular conduction is the usual cause of left axis deviation rather than ventricular displacement or hypertrophy. Grant stated: It is believed in the vast majority of cases of marked left axis deviation a left ventricular parietal block is responsible, resulting from a disturbance of conduction in the anterior division of the left bundle.[9] To this same cause Simson and Bruce[11] attributed the leftward deviation of the mean and terminal 0.04 second QRS forces encountered by them during transventricular aortic commissurotomy. Uhley and Rivkin[1] have published electrocardiograms recorded before and after focal septal incisions made through an apical ventriculotomy under conditions of total cardiopulmonary bypass. These authors reported superior displacement of undelayed terminal vectors after anterior division transection and normally placed but delayed terminal vectors after posterior division transection.

Data reported herein extend and modify our earlier reported observation that septal laceration in canine hearts produced no significant change in either QRS duration or axis[1] and the still earlier conclusion that extensive subendocardial lesions involving the apical half of the left ventricular septum and free wall did not produce evident prolongation of the QRS interval.[12] The type of anterior septal lesion pictured in Fig. 3 (under the heading *Anterior septal laceration attended by minimal axis shift*) commonly was attended by the appearance or slight deepening (less than 2 mm.) of a Q wave in Lead I and by a comparable degree of deepening of S in Leads III and aVF. The terminal R in Lead aVL often increased in height by 1 or 2 mm. Correspondingly limited changes in frontal plane forces attended severance of the posterior fibers of the left bundle branch, but these changes were consistently different from those produced by anterior septal laceration.

That greater shift to the left of the QRS axis may occur after some instances of anterior septal laceration is supported by findings presented in Figs. 5, 10, and 11. The cause of this greater shift may be sought in environmental factors, in the specific nature of the septal laceration, or in some combination of both. That environmental factors may render more evident the degree of shift produced by a specific septal lesion is supported by changes which attended closure of the chest as depicted in Figs. 10 and 11. However, such environmental alteration did not affect any one component of that complex preferentially. As S in Lead aVF deepened, R in that same lead increased, and the mean electrical axis remained unchanged. Moreover, care was taken throughout this study to insure constancy of the relationship between the cardiac surfaces and the extremities of the body. Major differences in electrocardiographic effects produced by anterior septal laceration, as those differences are reflected in the illustrations of this paper, probably derived from intrinsic cardiac factors and specifically from the nature of the septal laceration.

We have concluded that the degree of left axis shift produced by anterior septal laceration depends significantly on the degree to which the laceration isolates the anteriorly oriented hemisphere of the left ventricle from the normal rapid spread of excitation over subendocardial pathways. The greatest shift in axis and, relevantly, the most widespread delay in arrival of excitation at the anterior surface of the left ventricle, as determined by direct epicardial leads, resulted from a lesion like that shown in Fig. 5. Such a lesion has two significant features. These are: (a) interruption at a point high on the left side

of the septum of all save the most posteriorly placed fibers of the left bundle branch, a subtotal lesion, therefore, including all of the anterior and medial rami of that branch; (b) interruption of connections of the remaining posterior rami of the left branch to the mid septal network, a severance accomplished by extending the septal laceration from base to apex. The latter, however, is a feature of lesser significance than that noted under a.

Still nothing approaching a degree of left axis deviation which would be clinically significant in the human being has resulted from any of the various kinds of septal lacerations that we have produced in canine hearts. Nor was the limited left axis shift that resulted from anterior septal laceration in such hearts increased appreciably by the creation of intramural block in the free wall of the left ventricle[1] or by the induction of incomplete block in the main stem of the left bundle branch.[1] Work in progress strongly supports the judgment that the canine heart, as contrasted with the primate heart, is less subject to the development of left axis deviation and that this limited susceptibility derives not alone from recognized differences imposed by the artificial cardiac environmental conditions existing during experimental studies but also from species peculiarities in the distribution of the pathways of rapid subendocardial excitation.

Summary and conclusions

By means of appropriately placed ligatures, septal lacerations were produced in unopened canine hearts in situ. Electrocardiograms recorded before and after each such procedure were evaluated in relation to the anatomic lesion observed at necropsy. Small but definite changes in QRS axis distinguished interruption of anterior fibers from interruption of posterior fibers of the left bundle branch. Anterior septal lesions commonly were attended by the appearance or slight deepening of a Q wave in Lead I, by deepening of the S waves in Leads III and aVF, and by an increase in the terminal R wave in Lead aVL. Posterior septal lesion commonly produced loss of usually small S waves in Leads III and aVF and of the terminal R wave in Lead aVL. No remarkable further change of axis accompanied closure of the chest or healing of the laceration. Accepted electrocardiographic criteria for clinically significant left axis deviation were never satisfied. Complete transection of all left bundle branch fibers at mid septal or high septal level resulted in left bundle branch block.

QRS complexes in direct epicardial leads from regions of the ventricular wall to which excitation had been rendered aberrant by the septal laceration were altered characteristically and consistently as follows: (a) Delay in occurrence of intrinsic deflection. A lesion dividing either the anterior or the posterior portions of the left branch system caused a maximal delay approximating 20 msec. in the appearance of the intrinsic deflection. (b) Increase in R/S ratio. (c) Appearance of a Q deflection or widening and/or deepening of a preexisting Q. Lesser reciprocal changes were observed in complexes recorded from points on opposite epicardial surfaces.

The greatest shift in mean electrical axis in conventional leads and the most widespread delay in the appearance of intrinsic deflection in QRS complexes of direct epicardial leads were both produced by an anterior septal laceration characterized by subtotal interruption of all but high posterior fibers of the left bundle branch system. This limited degree of axis shift in the canine electrocardiogram produced by such a maximally effective lesion has afforded stimulus for study of species differences in electrocardiographic consequences of such lesions between canine and primate hearts.

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The radioisotope renogram in dogs with experimental renal artery stenosis

*Paul E. Wisenbaugh, M.D.**
Richard F. Clark, B.S.
Noah E. Wills, M.D.
Roger W. Jelliffe, M.D.
Cleveland, Ohio

The radioisotope renogram was introduced in 1956 as a method of study of differential renal function and has found its greatest use in the evaluation of patients suspected of having renal artery stenosis causing hypertension. It has been suggested, however, that the occurrence of false negative tests, lack of reproducibility, and the effects of primarily nonrenal factors preclude use of the procedure as a general screening test.[1-3] The present study was undertaken to investigate the sensitivity of the radioisotope renogram to changes in renal arterial circulation in dogs after the experimental production of stenosis of the main renal artery and to evaluate the reproducibility of serial observations made in each of the several phases of the study. The use of animals presents obvious advantages in that concern for the effects of specific or whole body radiation is eliminated and the lesions to be studied can be produced in a semiquantitative manner in a form uncomplicated by physiologic factors which might be associated with the spontaneous development of the lesions.

Since renal scintiscans have also been advocated as being useful in the diagnosis of renal vascular disease in human beings, postoperative renograms and scintiscans were compared to determine whether the combined use of these two techniques offered advantages over the application of either one alone. To aid in the evaluation of the radioisotope procedures, aortograms were recorded in each dog. Histologic studies were made of the ischemic kidneys of 2 of the dogs.

Methods

Adult mongrel dogs weighing 18 to 27 kilograms were used for this study. Sodium pentobarbital, 30 mg. per kilogram intravenously, was the anesthetic agent for all procedures including renograms.

Two stage constriction. An average of 7 individual renograms were recorded over periods of from 16 to 71 weeks for each of 5 normal dogs and served as controls in the evaluation of postoperative renograms. An open Goldblatt clamp was placed on the left main renal artery as close to the aorta as possible through a retroperitoneal approach. Postoperative renograms were recorded for 3 to 12 weeks. At a second operation the clamps were partially closed. An average of 5 additional renograms were then recorded over the ensuing 8 to 14 weeks, starting 1 week after narrowing of the clamp.

Single stage constriction. Subsequent to

From the Medical Service [illegible] Service, Veterans Administration Hospital, and Department of Medicine, Western Reserve University, Cleveland, Ohio.
Received for publication July 13, 1964.
*Address: [illegible] Hospital, [illegible] Cleveland, Ohio 44106.

the above described surgical procedures the renograms recorded over the 8 to 14 week period served to establish controls for the evaluation of postoperative changes in the right renogram. In a sixth additional normal dog, 10 control renograms were recorded in a period of 14 weeks. The right main renal artery of the 5 dogs and the left main renal artery of the sixth dog were constricted in a single stage operation. Renogram scintiscans and aortograms were then obtained during the next 13 months.

In order to estimate the degree of arterial constriction produced at operation, the area of the lumen of each clamp was measured prior to its insertion for each full turn of the adjusting screw. At the time of production of stenosis the clamps were adjusted in the following sequence counting the number of turns of the clamp adjustment screw required to achieve each successive position of the clamp. First the area of the lumen of the clamp was determined with the clamp in place around the artery in such a way as to gently contact the vessel wall but to produce only negligible constriction of the vessel (L). This was assumed to be that of the unconstricted artery. The clamp was next momentarily completely closed on the artery. The cross sectional area in that position (L) was assumed to represent that of the vessel wall. Finally the clamp was partially opened to produce the desired degree of stenosis. From the area of the lumen of the clamp in the final position (L) and those areas previously determined (L and L), the ratio of the differences representing the estimate of the per cent reduction in cross sectional area (RCA) of the partially constricted artery was calculated as follows:

$$\text{RCA} = \frac{(L_o - L\ )}{(L_o - L\ )} \times 100$$

In the production of stenosis of an artery by use of a Goldblatt clamp the original circular cross sectional shape of the artery is deformed. Such deformation is likely to produce more interference with circulation through the vessel than would stenosis which leaves the original cross sectional shape relatively intact. Nevertheless the foregoing estimate of the degree of stenosis was considered to be a reasonable approximation.

In the experiments with single stage constriction, in order to further evaluate the circulatory change produced by a given degree of stenosis, the pressure gradient between the aorta and the renal artery distal to the clamp was measured with a mercury manometer. These measurements are reported as per cent reduction in mean pressure (RMP).

During a period from 7 months prior to the first surgical procedure to 4 months after the last operation the mean systemic arterial blood pressure of each dog was measured twice weekly by femoral artery puncture using a 20 gauge needle and a mercury manometer.

Aortograms were obtained 6 to 12 months after single stage surgery by retrograde femoral artery catheterization with the tip of the catheter fluoroscopically positioned between or just below the orifices of the renal arteries. A single film was taken after 12 to 15 ml of a total dose of 20 ml of 50 per cent sodium diprotrizoate was manually injected.

The procedures for recording renograms were started approximately 30 minutes after induction of anesthesia. A polyethylene catheter was inserted into the dog's jugular vein through a 15 gauge needle and connected to a syringe by a 20 gauge needle. The animal was placed prone on a V shaped board. All tracer doses were made up to a total volume of 1 ml with normal saline, injected rapidly and immediately washed in with an additional 2 to 4 ml of normal saline.

After the injection of a 3 μc dose of sodium orthoiodohippurate I^{131} †, the probes oriented as nearly perpendicularly as possible to the transverse plane of the dog were positioned over the region of greatest detectable radioactivity in the renal areas. A 20 μc dose of Hipputope was then introduced and the radioisotope renograms were recorded over a period of 12 to 30 minutes. Tests were occasionally repeated 20 minutes or more after the previous injection.

The detection system for the renograms

* M k M Biedrack Chemical W ks, St Lo M
† Hippurope E R Squibb & So I New Y k N Y

consisted of a pair of probes equipped with 1½ by 1 inch sodium iodide crystals and 1½ by 4 inch straight bore collimators with no added filtration. A common high voltage power supply partially attenuated to accommodate any dissimilarity in characteristics of the probe phototubes and two precision rate meters with input sensitivity of 250 kv were used. Renograms were recorded with a time constant of 1.5 seconds on synchronized strip charts operated at speeds of ¾ inches per minute. The maximum response of the detectors was matched daily by placing the counter heads equidistant from a source of I^{131} contained in a 100 ml flask and adjusting the interdynode potential of one probe. The operating potential of the other unit was fixed throughout the entire series of observations. Since this procedure does not necessarily equalize integrated total response to scattered radiation and since it does not compensate for long term changes in response of the probes and rate meters, variation in absolute amplitude could be expected from one experiment to another. In the actual experiments variations from the mean of multiple readings obtained from a given kidney over a period of weeks or months were as great as 40 per cent in 2 dogs and 30 per cent in several others. Despite such inconstancy in absolute amplitude the ratio between peak amplitudes of the right and left kidneys remained relatively constant. In 50 control renograms the correlation coefficient was 0.75 ($p < 0.001$).

Because of the inconstancy in absolute amplitude it appeared to be unwise to evaluate postoperative curves in terms of the preoperative renogram obtained on the same kidney. The observed stability of the ratio between the two kidneys led to the adoption of a procedure which would use the opposite kidney as a standard of comparison. Curves for the left kidney before and after constriction of the left renal artery were reconstructed by expressing each point on a given curve as per cent of the maximum height of the simultaneously recorded curve for the right kidney. Postoperative curves from the left side could thus be compared to preoperative curves of the left kidney via the mediation of concurrent right peak values as contemporary standards.

In the 5 dogs which were originally subjected to two stage constriction on the left, renograms recorded throughout the period between left and right constriction showed that the ratio of preoperative right to stabilized postoperative left maximum values was relatively constant. Therefore the same principle used in evaluating postoperative changes in the left renogram was applied to the right. In this instance the control right renograms recorded in the interim between left and right constriction were redrawn in terms of per cent of the peak value of the corresponding curve for the left kidney. Thus comparison of postoperative with preoperative curves was again accomplished through the use of the contralateral kidney as a contemporary standard.

Repeated renal scintiscans were obtained on each dog during the period from 1 to 24 weeks after final operation using a dose of 50 to 100 μc of Hg^{203} chlormerodrin. The scanner was a conventional mechanically recording model equipped with a 3 inch diameter sodium iodide crystal 1 inch thick and a 19 hole focusing collimator. A dual channel amplifier provided individually variable background elimination and contrast enhancement.

Results

Preoperative controls. The broad shaded curves on the renograms of Figs. 1-6 represent one standard deviation above and below the average control renogram for each of the 6 dogs. Although even a simplified quantitative analysis of the renogram falls outside the scope and purpose of this paper, the significance of various characteristics of the curves can be qualitatively assigned. The 30 minute renogram in its simplest form may be considered to consist of four functions representing initial mixing and distribution of tracer throughout the systemic circulatory system, equilibration of tracer between blood and noncirculating body fluid pools, renal tubular secretion, and urinary excretion from the kidneys. In the typical renogram the first rapidly rising segment is largely the result of the

[illegible]

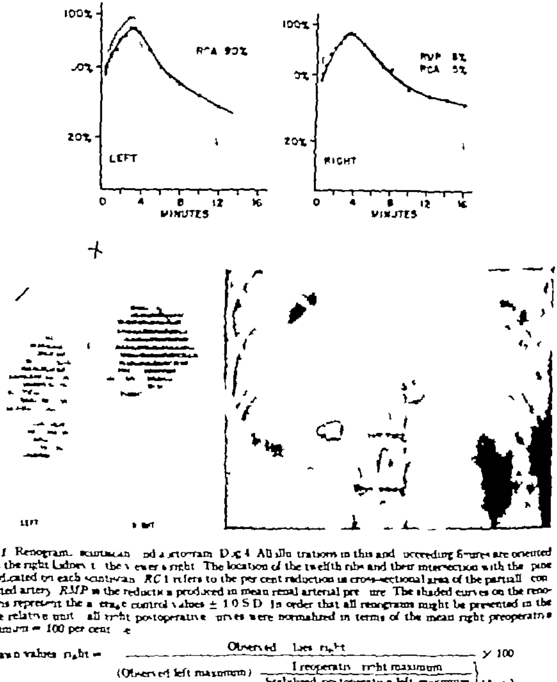


Fig. 1 Renograms, scintiscan and aortogram Dog 4. All illustrations in this and succeeding figures are oriented with the right kidney to the viewer's right. The location of the twelfth ribs and their intersection with the spine is indicated on each scintiscan. *RCA* refers to the per cent reduction in cross-sectional area of the partially constricted artery. *RMP* is the reduction produced in mean renal arterial pressure. The shaded curves on the renograms represent the average control values ± 1.0 S.D. In order that all renograms might be presented in the same relative units, all right postoperative curves were normalized in terms of the mean right preoperative maximum = 100 per cent, i.e.

$$\text{redrawn values right} = \frac{\text{Observed values right}}{\left(\text{Observed left maximum}\right)\left\{\dfrac{\text{Preoperative right maximum}}{\text{Stabilized postoperative left maximum}}\right\}_{(\text{Avg.})}} \times 100$$

The single superimposed curve on the left is the average of 5 renograms recorded 1 to 13 weeks after two-stage constriction of the left main renal artery but prior to constriction of the right. The solid curve on the right is the average of 7 renograms observed 1 week to 13 months after single-stage constriction of the right main renal artery. The S.D. of these and similar curves in succeeding figures is not significantly different from that of the control. Note the apparent reduction in concentration of Hg^{203} in the left kidney in the scintiscan recorded 10 weeks and 1 week after constriction, respectively, of the left and right renal arteries. The aortogram was obtained 10 months after constriction on the right and shows no significant difference between the kidneys in the concentration of contrast medium.

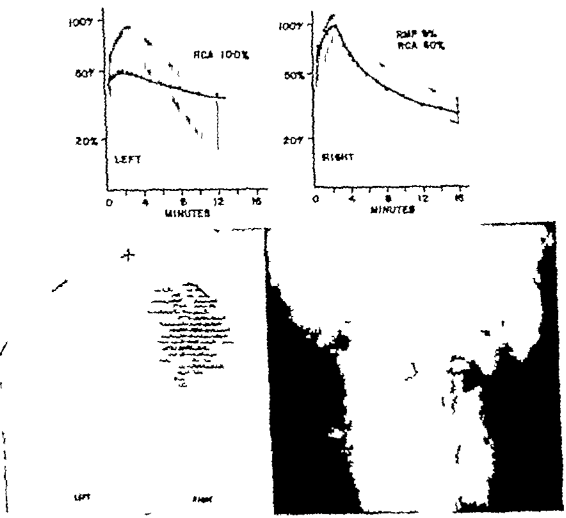


Fig 2 Renograms, scintiscan and aortogram Dog 1 The postoperative left renogram is the average of 5 renograms recorded 1 to 14 weeks after two-stage constriction The postoperative right renogram is the average of 6 renograms recorded [illegible] weeks to 10 months after single stage constriction on the right The scintiscan was recorded 7 and 4½ months after constriction respectively of the left and right renal arteries The aortogram was obtained 11 months after constriction on the right Note the marked reduction in left kidney function suggested by the scintiscan as compared to the degree of function suggested by the renogram and aortogram

filling of the vascular bed in the field of view of the detector within the first few seconds after injection The second more slowly rising portion of the curve is primarily a function of the rate of extraction of tracer material from the blood and secretion into the lumen of the renal tubule by the tubular epithelium The maximum value is attained when the rate of urinary excretion surpasses the rate of accumulation in the kidney The slope of the final segment reflects the limiting rate in the entire system and is usually determined by the rate of re-entry of tracer into the systemic circulation from extracirculatory body fluid pools

Two stage constriction Beginning approximately 1 week after placement of the open clamp on the left main renal artery of each of 5 dogs bilateral renograms were recorded for each dog in the group for comparison with the respective control values No significant postoperative changes occurred in 4 of 5 dogs The renogram of Dog 4 however showed a flattened peak and reduced slope in the final phase These abnormalities disappeared within 6 weeks after operation

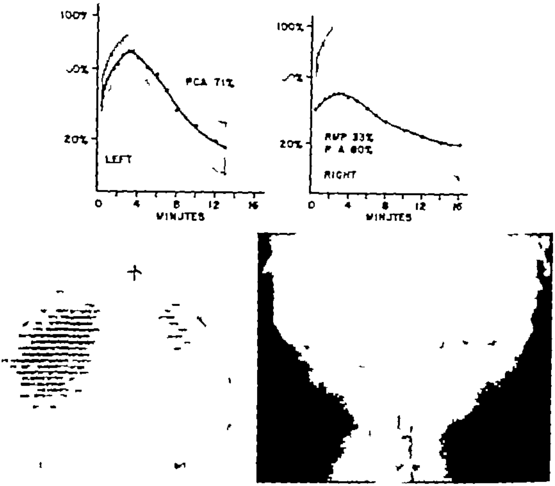


Fig 3 Renogram, scintiscan and aortogram Dog 5 The postoperative left renogram is the average of 8 renograms recorded 1 to 13 weeks after two-stage constriction The postoperative right renogram is the average of 11 renograms recorded days to 10 months after single-stage constriction on the right The scintiscan was recorded 9 and 5½ months after constriction respectively of the left and right renal arteries The aortogram was obtained months after constriction on the right The abnormality on the right is readily detected by each method used

During this period the dog demonstrated a moderate elevation in mean blood pressure of 25 to 30 mm Hg This elevation disappeared as the renogram returned to the control value

Three to 12 weeks after placement of the open clamps the dogs were reoperated upon and the clamps were closed to a different predetermined degree in each dog A reduction in cross-sectional area ranging from 30 to 90 per cent in Dogs 2 3 4 and 5 produced no significant changes in their renograms (Figs 6 5 1 3) A reduction in cross-sectional area of 100 per cent in Dog 1 produced the effect illustrated in Fig 2 wherein the curve is reduced in amplitude and flattened with a marked reduction

Table I Calculated reduction in cross sectional area of the lumen of the renal artery (RCA) and the observed reduction in mean renal arterial blood pressure (RMP)

Dog number	RCA	RMP
	Per cent reduction	
4	55	<8
1	60	19
5	80	33
7	0	54
3	—	5
	90	>95

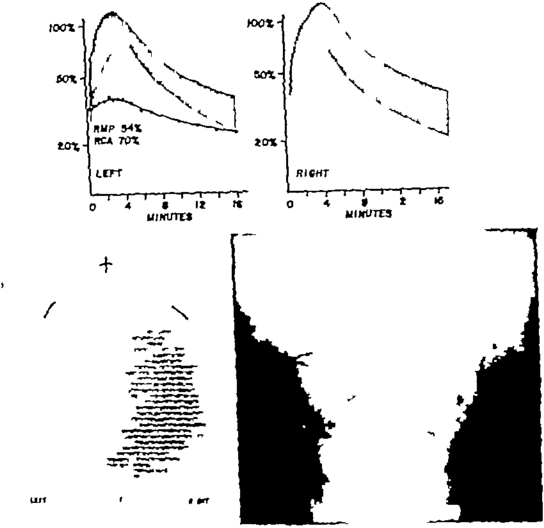


Fig 4 Renogram scintiscan and aortogram Dog 7 The postoperative left renogram is the average of 5 renograms recorded 7 days and 7 months after single stage constriction The scintiscan was recorded 3 weeks after constriction of the left renal artery The aortogram was obtained 6 months after constriction The scintiscan shows no detectable concentration of Hg^{203} in the left kidney even though the renogram shows definite function and the aortogram shows faint concentration of contrast medium in the left renal pelvis (arrow)

in the slope of the declining portion Although less severe than expected the renographic abnormality has persisted for a period of 13 months postatenosis The post constriction renograms are average curves based on 4 to 8 observations in each dog recorded over a period of 2 to 4 months beginning 7 days after operation

Single stage constriction Since the effect of constriction of the left main renal artery was less than anticipated for all degrees of stenosis the possibility existed that this reduced effect was partially due to the development of a readily available collateral circulation between the first and second operations In an attempt to minimize this the right main renal arteries of the 5 dogs with left renal artery stenosis of 2 to 4 months duration and the left main renal artery of 1 dog not previously subjected to operation were constricted with Goldblatt clamps in a single stage operation The mean pressure gradients thus produced were measured at the time of operation

Table I shows the estimated reduction in cross sectional area of the artery and the resulting reduction in mean perfusion pressure The effect of this procedure on the renograms is shown in Figs 1 6 A

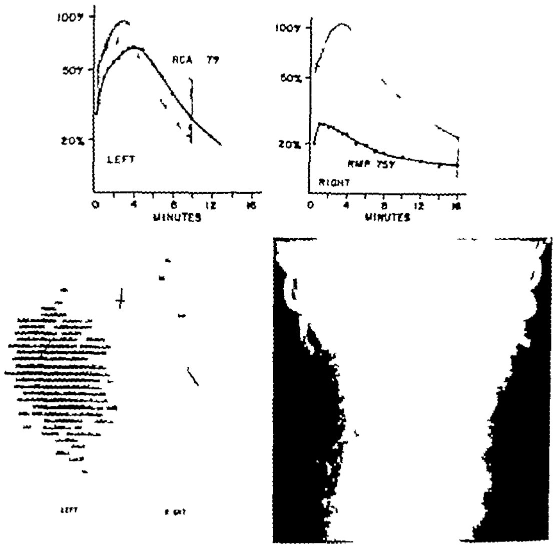


Fig. 3. Renogram, scintiscan, and aortogram Dog 3. The postoperative left renogram is the average of 3 renograms recorded 1 to 10 weeks after two-stage constriction. The postoperative right renogram is the average of 11 renograms recorded 1 week to 17 months after single-stage constriction on the right. The scintiscan was recorded 16 and 4 weeks after constriction, respectively, of the left and right renal arteries. The aortogram was obtained 17 months after constriction on the right. The renogram reveals slight remaining kidney function which is not demonstrated by the other methods used.

reduction in pressure of approximately 10 per cent had little or no effect on the renogram (Figs. 1 and 2), whereas a reduction of 33 per cent or more produced abnormalities which persisted during a period of 7 to 13 months of observation and were roughly proportional to the severity of stenosis (Figs. 3-6). The major change was a reduction in amplitude of the early portion of each curve. However, because of a decrease in slope of the late declining segment of the curves, the amplitudes after 12 minutes were within the range recorded in the normal control renograms. A significant reduction in the slope of the second rising component of the curves was also noted. The curve of Dog 2 is quite similar to that recorded over any nonspecific tissue (Fig. 6). The postconstriction renograms illustrated are average curves of 5 to 11 tests recorded in each dog over a period of from 2 days to 13 months after operation.

On at least three separate occasions, randomly chosen from 1 to 24 weeks after the last surgical procedure, both bilateral

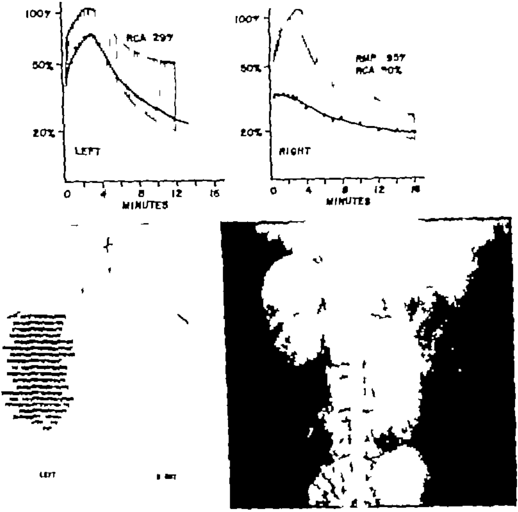


Fig 4 Renogram scintiscan and aortogram Dog 7 The postoperative left renogram is the average of 4 renograms recorded 3 to 8 weeks after two-stage constriction The postoperative right renogram is the average of 6 renograms recorded days to 11 months after single-stage constriction on the right The scintiscan was recorded 8 and 6 months after constriction respectively of the left and right renal arteries The aortogram was obtained 12 months after constriction on the right There is no evidence of function of the right kidney by any of the method used The time of peak concentration over the right kidney is the same as that over any non specific tissue

renograms and a scintiscan were recorded sequentially on each dog No progressive changes were apparent in either type of test In general the scintiscan showed less uptake of labeled chlormerodrin than might be expected from the level of renal function indicated by the corresponding renogram (Figs 1 6) With the single exception of Dog 3 (Fig 5) aortograms obtained 6 to 12 months after final operation revealed blood flow to every kidney that showed function by renography even though there was no detectable concentration of the mercury isotope on the scintiscans (Figs 1 6)

At autopsy the right kidney of Dog 3 was markedly atrophic and scarred A sagittal section of the whole kidney showed that in areas in which nephrons were preserved the ratio of tubules to glomeruli was normal or greater than normal However the tubules were dilated had flattened epithelium and contained pink staining casts (Fig 7 1) In contrast the right kidney of Dog 2 showed no postoperative function by any of the tech

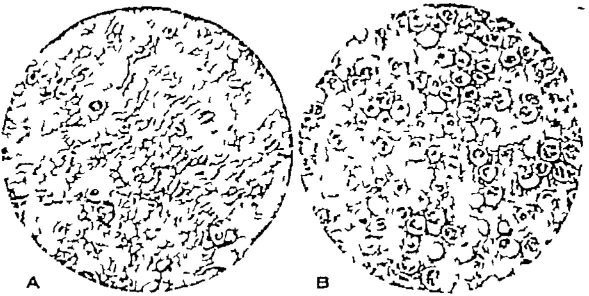


Fig. 7 Renal parenchyma of Dog 3 (A) and Dog 2 (B). Note the greater preservation of tubules in A. Hematoxylin and eosin stain. ×100

niques used. At exploration and excision this kidney was slightly more atrophic and histologically showed marked crowding and dilatation of glomeruli with a marked diminution in the number of tubules (Fig. 7 B).

Significant changes in blood pressure occurred in only 3 dogs during the period of observation. In only one instance, that of the minimal constriction of the right renal artery in Dog 1, did the procedures which produced the rise in blood pressure fail to produce an abnormal renogram. In this animal the previous constriction of the left renal artery had produced hypertension which lasted approximately 8 weeks and after the slight narrowing of the right renal artery she again became hypertensive.

Discussion

Spencer, Callendine and Vincent[4] studied the reproducibility of I[131] Diodrast renograms in 4 normal human beings and concluded that the absolute amplitude of the renogram showed the greatest variation, that variation in configuration was somewhat less, and that these findings were probably due chiefly to difficulty in positioning the detector probes. In the present series the greatest variation in the control renograms was also in absolute amplitude. The peak time and the slopes of the rising and declining portions of the curves were quite reproducible. It is thought that the method of positioning the probes using a small locating dose has considerable advantage over other methods which might be used, and in this series minimized this source of error.

The significant variations in absolute amplitude which remain after matching the probes and optimizing probe position by use of locating doses of tracer material make the evaluation of a given renogram difficult when attempts are made to compare its absolute values with those of a renogram recorded some time earlier over the same kidney. That the factors which produce the major fluctuations in amplitude affect both renograms simultaneously and to a remarkably similar extent is supported by the good correlation observed in the series of renograms recorded on normal dogs. Thus the method of analysis wherein one kidney serves as a contemporary standard for the opposite experimental kidney enables comparisons to be made with a much greater degree of confidence.

Renography, therefore, is a convenient method of evaluating the difference in function between two kidneys, even over widely spaced intervals of time, although

no normal absolute values can readily be established for the individual kidneys. Through the use of commonly available equipment and with the technique described above wherein all values of both renograms are computed in relation to the maximum of the renogram of greater amplitude, differences in slopes and peak times as well as amplitude can be evaluated. Block and associates[7] have used somewhat the same principle by recording a renogram over one kidney and with a ratio detector simultaneously and continuously recording the ratio of the counting rate of the other kidney to the sum of the counting rate of both kidneys.

Klapproth and associates[8] and Winter[9] showed that the ligation of one branch of the main renal artery reduces the amplitude of the renogram with little change in configuration. DeMaria and co-workers[9] noted that with resection of 50 per cent or less of the dog kidney there was little or no effect on subsequent I^{131} Diodrast renograms unless these were recorded during saturation of the tubular mechanism with PAH. Stewart and Haynie[3] made similar observations in human patients with segmental arterial disease: only 2 of 5 such patients had abnormal renograms. This might be expected since perhaps 50 per cent of the renal parenchyma would function normally, and in chronic experiments such as those described by DeMaria and co-workers,[9] there might be compensatory hypertrophy and an increase in function of the remaining tissue such as occurs in dogs after unilateral nephrectomy.[10] Sharpe and associates[11] reported that acute constriction of the main renal artery in dogs with pressure gradients of less than 50 mm. Hg produced only prolongation of the terminal phase of the renogram, whereas pressure gradients of more than 55 mm. Hg produced a reduction in amplitude, broadening of the peak, and a marked prolongation of the terminal phase. In our experiments renograms recorded within 2 hours after operation sometimes showed marked abnormalities which did not correlate with the degree of constriction and were thought to be related to trauma to the kidney during operation in that they did not persist. Only changes such as those demonstrated in the one instance of delayed closing of the clamp and those occurring in 4 of the 6 instances of the production of stenosis by a single-stage procedure were considered to be significant in that they were permanent. Of the mean gradients measured in 6 of the experiments, the smallest associated with a significant change in the renogram was 40 mm. Hg. The pressure gradients producing abnormal renograms in these dogs may be compared with the systolic pressure gradients reported by Spencer and associates[1] in 17 patients with hypertension and renovascular occlusive disease. The values in their patients ranged from 45 to 210 mm. Hg, with all but one being at least 70 mm. Hg.

Of the procedures used for the diagnosis of renal vascular disease, Haynie and associates[4] rank the Hg^{203} labeled chlormerodrin scintiscan as second only to the aortogram. Our results in dogs support this view to the extent that the uptake of chlormerodrin was less than expected from the appearance of the concurrent renogram. In 2 instances (Figs. 4 and 5) the scintiscan showed no uptake at all, although the renograms and other studies showed the presence of remaining renal function.

The renogram is of significant value because of its ability to reveal function in a kidney at levels below that at which detectable chlormerodrin concentration occurs, since such a kidney remains suspect as a cause of hypertension, whereas a nonfunctioning kidney probably does not produce hypertension. This ability of the renogram is illustrated by a comparison of Dogs 2 and 3. The postconstriction right renogram of Dog 2 (Fig. 6) is similar to a curve obtained over any nonspecific tissue of the body, whereas the postoperative right renogram of Dog 3 (Fig. 5) shows minimal but definite uptake and excretion of tracer. These results are consistent with the histologic difference found between the kidneys. The relatively greater preservation of tubules in the kidney of Dog 3 would be expected to result in some extraction of Hippuran by this kidney. That this compound is mainly cleared from the plasma by renal tubular epithelium is shown by the ability of PAH to interfere with its uptake by the kidney.[4]

These results indicate that renogra-

and scintiscanning are complementary and that the two procedures together give information which neither used alone can invariably supply. It is suggested that the routine screening of hypertensive patients can be satisfactorily accomplished by combining both these procedures with standard radiologic techniques. With the use of currently available short-lived Hg[203] chlormerodrin for scintiscanning, both renography and scintiscanning may be safely performed without the risk of significant whole body or kidney radiation exposure. Thus if a hypertensive patient has kidneys which are shown to be normal and equal in physical size and equal in function and functional size, additional more traumatic studies would not usually be necessary.

That there were few instances of elevation of the blood pressure in these animals is of interest. Recently, Blaufox and associates[13] have reported that the radioisotope renogram is normal in unilaterally nephrectomized dogs after the onset of experimental renal hypertension without uremia but is abnormal in those animals which develop uremia in addition to hypertension. These workers produced hypertension by constriction of the main artery of the remaining kidney using a polyvinyl clamp. In our experience, the degree of constriction they produced as judged by their description of the change in the diameter of the renal artery would not usually alter the renogram in intact *animals*.

The present demonstration of alteration in the renogram in the absence of hypertension in some animals is not necessarily at odds with the findings of Blaufox and associates.[13] The degree of unilateral constriction required to produce hypertension in an intact dog is extremely critical, and even when hypertension results it is usually transitory.[14] In addition, the presence of a normally functioning opposite kidney will tend to raise the threshold for the production of hypertension by renal ischemia.[15] Thus an abnormal renogram in the absence of hypertension is not surprising. In contrast to the experimental situation in the dog, however, it has been repeatedly observed in human beings that unilateral renovascular disease can produce chronically sustained hypertension, sometimes of severe degree.[1] It is even more remarkable that this occasionally occurs with involvement of only one segmental renal artery.

Conclusions

1. Acute constriction of the main renal artery in dogs which produces a reduction of at least 33 per cent in mean blood pressure to the kidney produces permanent abnormalities in the radioisotope renogram which are generally proportional to the resulting pressure gradient.

2. The radioisotope renogram may reveal function in a kidney which does not concentrate sufficient labeled chlormerodrin to produce a meaningful scintiscan pattern or enough contrast material to produce a nephrogram effect during aortography.

3. The radioisotope renogram is a useful procedure for the evaluation of remaining renal function in patients with known or suspected renal vascular lesions. Combination with scintiscanning techniques would further enhance its usefulness and is recommended.

4. Use of a small locating dose of tracer material appears to be of significant value in optimizing the detector position, thereby minimizing this source of variations in amplitude of the renograms.

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Circulatory and ventilatory responses to postprandial exercise

W. B. Jones, M.D.
H. D. Thomas, M.D.
T. J. Reeves, M.D.
Birmingham, Ala.

A change in the cardiovascular and ventilatory responses to exercise after a heavy meal is a generally accepted phenomenon. An early observation relating to this was made by Heberden in the eighteenth century.[1] He noted an increase in the susceptibility to angina pectoris occasioned by exercise after a meal. More recent investigations have demonstrated an increase in resting heart rate and a decreased tolerance to exercise after meals.[2] However, little physiologic data are available in man on which to base an explanation for these findings. Grollman and Gladstone found that a heavy meal increased the heart rate and also increased the cardiac output by 30 to 50 per cent within 20 minutes after the midpoint of a meal.[3,4] Both of these investigations were carried out using the acetylene method of determination of cardiac output. No studies using more modern methods could be found in the literature relative to the cardiovascular and ventilatory responses to the postprandial state. Recent physiologic studies suggest that a meal has some effect on myocardial oxygen metabolism. Regan and associates[5] reported that a high fat meal resulted in a decrease in myocardial oxygen consumption relative to mechanical work of the heart. They postulated that postprandial lipemia interfered in some manner with oxygen transport to the myocardium.

The postulate prior to this study was that there were three possible changes that might occur after a meal. The first possibility was that purely hemodynamic changes might occur, such as an increase in cardiac output, arterial pressure, or mode of ejection. The second consideration was that the postprandial "alkaline tide" might result in a decreased oxygen pressure at capillary level. The interference with oxygen transport as postulated by Regan was a third possible mechanism. This study was designed to investigate further these possibilities and any changes in hemodynamics and blood gases occurring after meals which might affect myocardial oxygen demand or oxygen availability. The experimental design called for measurement of a number of hemodynamic variables, blood gases, and pH at rest and during exercise in fasting and postprandial subjects. Arterial blood lactate and pyruvate concentrations were also determined under these conditions as an index of the over-all effectiveness of oxygen transport in the body.

From the Department of Medicine, Medical College of Alabama, and the Medical Service, Veterans Administration Hospital, Birmingham, Ala.
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Address: Medical College of Alabama, 1919 Seventh Avenue South, Birmingham 3, Ala.

Method

Five normal young adult males were studied at rest and during exercise before and after a test meal. Five similar subjects were studied according to the same protocol, except for the omission of the meal. The subjects studied without the meal were included in order to minimize the possibility of ascribing changes due to the procedures themselves to the effect of the meal. The age range of the subjects was 20 to 40 years.

Each subject came to the cardiac catheterization laboratory at 9:30 A.M., having fasted since the previous evening. A Teflon catheter was inserted into an antecubital vein and passed into the superior vena cava. A No. 6 Teflon aortic catheter, 80 cm. in length, was inserted percutaneously using the Seldinger technique into the left brachial artery and passed under fluoroscopic control into the ascending aorta. The catheter and manometer system has been found to be linear in phase and amplitude to between 20 and 25 cycles per second to a generated sinusoidal pressure. A mechanical damping device was employed to provide approximate optimum damping to a pressure square wave.

After the catheters were in place, a recording was made on a multichannel oscilloscopic recorder.* The recorded variables consisted of an electrocardiogram, aortic pressure, first time derivative of the aortic pressure, phasic blood flow, and the integral of aortic flow. The aortic blood flow as derived from the aortic pressure pulse has been described previously.[1,9] It was used in this study primarily to obtain the stroke volume at frequent intervals during the procedure. In each subject this method of determining stroke volume was calibrated by comparison with stroke volumes obtained by the dye-dilution method in the manner previously described. Although stroke volume was determined by this indirect method much more frequently than by the dye-dilution method, the correlation coefficient from the 55 paired values was 0.94.

After obtaining the aortic flow and pressure curves, the cardiac output was obtained using indocyanine green dye and a densitometer.* Ten milligrams of dye was injected into the subclavian vein and washed in with 10 c.c. of normal saline. Blood was withdrawn at 25 c.c. per minute from the aortic catheter through the densitometer with a constant speed withdrawal pump.† The volume of the aortic catheter and cuvette was found to be 1.5 ml. The dilution curve was recorded on the oscilloscopic recorder. The decay phase was extrapolated on semilog paper, and the area of the curve was determined by the trapezoidal method.

Simultaneous with the dye-dilution curve, expired gas was collected over a 3 minute period into a Douglas bag. This volume was measured in a Tissot gasometer and analyzed with the Scholander apparatus for oxygen and carbon-dioxide content. As soon as the dilution curve was completed, samples of arterial blood were withdrawn for analysis of oxygen content, carbon-dioxide content, pH, pO_2, pCO_2, lactate, and pyruvate. Oxygen and carbon-dioxide contents were determined on the Van Slyke apparatus. The pH, pCO_2, and pO_2 were measured using electrode techniques.‡ The pH was determined by using a gun capillary chain electrode.§ The CO_2 electrode was glass with a calomel reference electrode. Concentrations of lactate were measured by the Barker-Summerson method.[9] Concentrations of pyruvate were determined according to the Friedemann-Haugen technique.[10] The exact methods of collection and determination in this laboratory have been reported previously.[11]

Each of the resting determinations was duplicated and averaged. After the resting measurements were obtained, the subjects were exercised with a constant workload bicycle ergometer.¶ Exercise was performed for 5 minutes in the supine position. The bicycle resistance load varied in the subjects between 200 and 350 Kg.M. per minute according to the physical fitness of the subject. The load was chosen to be

*Electronics for Medicine, Inc., White Plains, N. Y.

*[illegible] C [illegible] SC 250 [illegible] N. Y.

†[illegible] C[illegible]bridge, Mass.

‡Beckman Phys[illegible] Gas Analyzer.

§pH Meter 22, Radiometer, Copenhagen, Denmark.

¶[illegible] and W. King Company, [illegible] Y.

‖[illegible]

a moderate stress. At half minute intervals the aortic pressure, heart rate, and computed variables were recorded. A 1 minute collection of expired air was made starting 3½ minutes after the beginning of exercise. While the expired air was being collected, a dye dilution cardiac output curve was obtained. Immediately after the cardiac output had been determined, blood was withdrawn for the determination of pH, pO_2, pCO_2, O_2 content, lactate, and pyruvate. A final recording of the hemodynamic variables was made prior to termination of the 5 minutes of exercise.

The subject was allowed to recover for 20 minutes. Again all hemodynamic and blood gas measurements were repeated. Each of the experimental subjects was now given a 1,000 calorie test meal. The meal consisted of a milk shake fortified with egg and powdered milk solids. The composition of the test meal was 30 per cent protein, 30 per cent fat, and 40 per cent carbohydrate. The 5 control subjects were given nothing at this time. Twenty minutes after completion of the meal (40 minutes after the end of the first period of exercise), each subject was again studied according to the same schedule as that used prior to the meal. The level and duration of exercise was unchanged for the two periods of exercise undertaken by each subject.

Results

The findings are particularly summarized in Tables I and II. The measured variables are discussed separately. The statistical method used was primarily that of analysis of variance.[1] A comparison of the experimental and control subjects was made as to the difference between the values obtained during the first period of rest and exercise and those obtained during the corresponding time in the second period. The method evaluates the probability of the differences in the two groups being random.

Cardiac output. In both control and test subjects the 40 minute recovery cardiac index was essentially the same as the initial resting value. Also there was no significant difference between the cardiac indices in the two exercise periods. All cardiac indices considered were obtained by the dye dilution method. The fed test subjects and the controls responded in a similar manner, suggesting that the meal produced no effect on this variable.

Heart rate. The heart rate at the end of the postprandial rest period was faster than the initial resting rate in 4 of 5 subjects. The average increase was 6 beats per minute. This may in part reflect incomplete recovery from the initial exercise period which, however, had been completed 40 minutes earlier. The control subjects showed a similar increase in rate (5 beats per minute). During the fourth minute of exercise all the fed subjects exhibited a faster rate during the postprandial period of exercise than during the fasting period of exercise. The average change was 10 beats per minute. The control subjects failed to exhibit this consistent difference in rate during the two exercise periods. Three had a slightly faster rate during the second exercise; in 2 the rate slowed. The average change was a decrease of 1 beat per minute during the second period of exercise. By analysis of variance this difference in response of the two groups is significant at the 90 per cent confidence level but not at the 95 per cent level.

Mean ejection pressure. The test meal had no statistically significant effect on the mean aortic ejection pressure either at rest or during exercise. This pressure was obtained by adding 60 per cent of the pulse pressure to the aortic diastolic pressure.

Duration of ejection. The duration of left ventricular ejection was obtained by measurement from the aortic pressure of the interval between the upstroke of the pulse and the incisural notch. The test meal resulted in a significant decrease in ejection time at rest and a statistically inconclusive decrease during exercise. The resting difference between the fed and fasting states is significant at the 95 per cent level.

Tension time index per beat. This index is the product of the mean aortic ejection pressure and the duration of ejection. There was an inconclusive decrease in this index during the postprandial exercise as compared to the second exercise of the control subjects. This decrease during the postprandial exercise was balanced by the increase in rate so that the minute tension

Table I*

	Group A† (fed subjects)		Group B‡ (control subjects)		Analysis of variance (Groups A and B) F
	Mean and SD	Range	Mean and SD	Range	
Cardiac index (L/min/M)					
Resting I	3 67 ± 55	2 86–4 35	3 06 ± 42	2 34–3 58	
Resting II	3 57 ± 49	2 87–4 36	3 06 ± 61	2 67–4 18	<1 0
Exercise I	7 36 ± 91	6 88–8 28	7 48 ± 1 77	4 92–9 57	
Exercise II	7 50 ± 89	6 88–8 50	7 55 ± 1 64	5 94–9 99	<1 0
Heart rate (beats/min)					
Resting I	68 ± 6	61– 81	72 ± 10	64– 92	
Resting II	77 ± 10	71– 96	75 ± 7	69– 89	<1 0
Exercise I	129 ± 21	100– 161	130 ± 13	108– 144	
Exercise II	139 ± 18	114– 168	129 ± 7	118– 139	4 7
Mean ejection pressure (mm Hg)					
Resting I	124 ± 6	112– 129	111 ± 14	92– 133	
Resting II	116 ± 10	103– 129	112 ± 14	97– 137	1 3
Exercise I	151 ± 15	131 173	156 ± 13	134– 170	
Exercise II	153 ± 16	133– 175	149 ± 18	122– 175	2 3
Duration of ejection (sec)					
Resting I	304 ± 010	284– 314	282 ± 023	242– 310	
Resting II	276 ± 018	245– 294	272 ± 017	245– 291	11 4§
Exercise I	239 ± 078	199– 257	229 ± 033	184 281	
Exercise II	209 ± 020	183– 236	221 ± 029	1 4 252	3 8
Tension time index/beat (mm Hg/sec)					
Resting I	33 7 ± 7 9	18 5–40 0	31 5 ± 6 5	21 6–37 8	
Resting II	30 4 ± 5 9	19 8–38 0	30 5 ± 3 3	27 0–35 8	<1 0
Exercise I	36 1 ± 1 7	34 1 38 6	34 5 ± 2 6	30 5–38 0	
Exercise II	30 8 ± 2 9	26 4–35 6	33 7 ± 5 0	27 9–42 9	4 3
Ventilation (L/min/M)					
Resting I	4 1 ± 1 0	2 5– 5 3	5 1 ± 1 7	3 3– 7 4	
Resting II	4 6 ± 1 4	2 4 6 4	4 4 ± 5	3 9– 5 2	1 6
Exercise I	18 3 ± 4 0	11 5–23 8	17 2 ± 2 3	14 5–20 9	
Exercise II	20 0 ± 4 4	11 7–24 2	16 4 ± 2 2	15 0–20 8	3 7

*The subjects are divided into two groups according to whether they did (A) or did not (B) receive a meal after the first period ... Resting I and Exercise I are ... both groups. Resting II and Exercise II are postprandial ... in Group A ... in Group B
†Resting I and Exercise I are fasting; Resting II and Exercise II are postprandial
‡All ... are fasting
§Greater than 95 per cent significance.

time index was essentially the same in the preprandial and postprandial exercise periods

Ventilation There was a slight but statistically insignificant increase in ventilation during the postprandial exercise

Oxygen uptake The oxygen consumption was significantly increased in the postprandial resting period The increase in oxygen uptake associated with the postprandial state is also seen in the exercise values but is statistically not so significant

Arterial pH There was no significant change in arterial blood pH after the test

Table II

	Group A (fed subjects)		Group B† (control subjects)		Analysis of variance (Groups A and B) F
	Mean and SD	Range	Mean and SD	Range	
O uptake (c /min /M)					
Resting I	142 ± 17	117– 169	142 ± 16	128– 170	
Resting II	161 ± 15	145– 187	141 ± 12	127– 157	6 6
Exercise I	772 ± 145	493 861	741 ± 85	610– 878	
Exercise II	820 ± 159	519– 938	717 ± 116	579– 905	2 9
Arterial pO					
Resting I	100 ± 7	91 112	93 ± 9	9 107	
Resting II	93 ± 9	87 105	94 ± 9	86– 111	<1 0
Exercise I	97 ± 9	85 113	97 ± 11	76– 106	
Exercise II	96 ± 9	85– 112	93 ± 11	9– 109	<1 0
Arterial pH					
Resting I	7 40 ± 0	7 38 7 43	7 38 ± 03	7 33 7 43	
Resting II	7 39 ± 03	7 38 7 45	7 38 ± 04	7 30–7 42	<1 0
Exercise I	7 32 ± 01	7 26–7 37	7 31 ± 05	25 36	
Exercise II	7 36 ± 03	7 31 7 39	7 35 ± 08	7 21 7 43	<1 0
Lactate (mM /L blood water)					
Resting I	76 ± 22	49 1 05	68 ± 15	57 96	
Resting II	1 29 ± 50	71 2 15	1 21 ± 45	68 2 03	<1 0
Exercise I	5 29 ± 1 78	3 40 8 61	5 72 ± 87	4 81 6 87	
Exercise II	6 22 ± 2 32	3 00–9 79	5 11 ± 84	4 07 6 61	4 9
Pyruvate (mM /L blood water)					
Resting I	106 ± 018	086– 118	090 ± 013	075– 101	
Resting II	120 ± 015	093– 151	127 ± 039	085– 177	<1 0
Exercise I	190 ± 017	166– 203	172 ± 031	177– 221	
Exercise II	136 ± 035	098– 179	161 ± 031	119– 199	4 1
Lactate pyruvate ratio					
Resting I	7 4 ± 2 6	4 1 10 5	7 6 ± 1 6	5 3– 9 5	
Resting II	11 0 ± 6 7	4 7–18 7	9 6 ± 1 7	7 7–11 8	1 0
Exercise I	28 1 ± 9 9	16 7–45 2	34 5 ± 7 8	21 8–44 9	
Exercise II	49 6 ± 32 5	16 8–92 4	37 8 ± 6 7	20 5–40	7 2‡

*Resting I and Exercise I are fasting Resting II and Exercise II are postprandial
†All values fasting
‡Greater than 95 per cent significance

meal as judged by a comparison of the value in the 40 minute postprandial period and the initial resting value Exercise produced the expected drop in pH The drop in pH in the exercising postprandial subjects was less marked than during the fasting exercise averaging a decrease of 03 instead of 08 However the control subjects also had less change during the second period of exercise (03 versus 07) The difference between the two groups was not significant

Lactate and pyruvate The concentrations of lactate at rest were increased slightly in the postprandial period However a similar increase was seen at the comparable time period in the control subjects This suggests an incomplete return of lactate to resting levels after the first period of exercise Such a slow

decline in lactate after exercise is consistent with previous observations.[11] After the second period of exercise the fed subjects exhibited a mean increase in the concentration of lactate of almost 1 millimole per liter of blood water, whereas the control subjects showed a slight decrease in comparison with the first period of exercise. The difference between the two groups was significant at the 90 per cent confidence level.

The resting concentrations of pyruvate showed a similar slight increase after the first period of exercise in both the fed and control groups. Exercise resulted in an increase in the concentrations of pyruvate. However, this increase was less marked in fed subjects during the second period of exercise. The difference was statistically significant at the 90 per cent level.

The lactate/pyruvate ratio was significantly greater during the postprandial exercise; the difference in the fed and control subjects was significant at the 95 per cent confidence level.

Discussion

The lack of a significant increase in cardiac output at rest or during exercise after a meal was surprising. The resting oxygen consumption increased by an average of 19 ml. per minute per square meter postprandially, indicating a slight widening of the arteriovenous oxygen difference. During exercise the oxygen consumption was slightly increased, as was the cardiac output, and the arteriovenous difference was not altered. Since the only previously reported studies of which we have knowledge showing an increase in cardiac output were carried out with the acetylene technique, the discrepancies may in part represent differences in the methods. It is also possible that a difference in the time of study might explain some of the variation, although Grollman reported an immediate rise in cardiac output that lasted 1 to 2 hours.

Since the arterial pressure was likewise unaltered by feeding, either with the subject resting or during exercise, the minute pressure-volume work was unchanged. The stroke work was slightly decreased. The tension-time index per minute was increased in proportion to the heart rate by exercise. This increase was not different after eating. The lack of influence of feeding on these variables requires other explanations for the well-established postprandial decrease in exercise tolerance in patients with angina pectoris.

The measurements of pH and pO_2 failed to show any demonstrable difference as a result of the meal. The pH at rest was unaltered. During exercise, the change in pH was the same in both the fed and unfed groups. Thus, the postulated postprandial alkalosis mechanism was not confirmed. Previous studies of this phenomenon have not included measurements of arterial pH. The increase in urine pH, the "alkaline tide," would not appear to have associated changes in blood concentrations of the hydrogen ion.

The measurements of arterial pO_2 are consistent with those of pH, since they fail to show a difference as a result of eating. The lack of significant change during exercise in the postabsorptive state is in agreement with the studies of Lilienthal and of Mitchell and their colleagues.[10,11]

The most marked alterations after a meal were the increase in heart rate, especially during exercise, the increase in lactate/pyruvate ratio during exercise, and the disproportionate decrease in the duration of ejection at rest.

The increase in heart rate during exercise has been a consistent finding in previous studies. The acceleration of the heart rate has been ascribed by LeQuesne and co-workers[14] to a decrease in effective blood volume averaging 5 per cent in normal subjects. The mechanism of this reduction remains speculative. The fluid is thought to be lost either into the lumen of the gut or into the mesenteric tissues and vascular network. Both LeQuesne[1] and Castenfors[16] reported a significant correlation between the increase in pulse rate and the decrease in effective blood volume. The hemodynamic changes found in the subjects comprising the study are like those that would be expected to follow a small phlebotomy. That is, the cardiac output and blood pressure are maintained but with an increased heart rate. Such an effect would be augmented by the actual volume of blood drawn for the various determinations. This averaged approx-

mately 100 c c However this volume was the same for both fed and control subjects

There is good evidence that the heart rate per se is an important determinant of the myocardial oxygen consumption per minute Katz and his colleagues have reported that the product of heart rate and mean arterial pressure has an excellent correlation with myocardial oxygen consumption over a wide range of variations in pressure and flow [7] If however epinephrine or calcium were infused into their experimental animals the amount of oxygen utilized by the heart was increased disproportionately to the increase in the product of the heart rate and blood pressure

Sarnoff and associates[11] have reported that the tension time index (time integral of the ventricular pressure pulse during ejection systole) is closely related to myocardial oxygen consumption They suggested however that this relationship might also be altered by inotropic interventions that would increase the rate of tension development In the present study the tension time index increased in proportion to the heart rate but was not different in the fed and nonfed groups In the fed subjects the relatively greater increase in heart rate was balanced by the greater decrease in the duration of ejection

Morris[1] has suggested that in addition to the changes after a meal that are consistent with a decrease in effective blood volume there is evidence of an adrenaline like effect This suggestion is based on a finding of an increase in renal blood flow occurring 20 to 30 minutes after a meal Indirect evidence is present in the data from this study suggesting a postprandial sympathomimetic effect In a previous study from this laboratory it has been demonstrated that the duration of left ventricular ejection can be predicted from the heart rate stroke index and the end-diastolic aortic blood pressure [8] The equation for this determination is as follows

$$\text{Duration ejection (seconds)} = .36646 - .00108\ (\text{rate}) - .00036\ (\text{diastolic pressure}) + .00076\ (\text{stroke index}) \quad (1)$$

The standard error of estimate is .016 second

The duration of ejection was predicted by the foregoing equation for the postprandial resting and postprandial exercise periods Data were obtained at 30 second intervals during the postprandial exercise period The stroke indices were obtained by the method previously described based on the aortic pressure pulse The predicted duration of ejection was plotted against the measured duration of ejection This is shown in Fig 1 The 95 per cent confidence bands shown in Fig 1 were obtained from fasting normal subjects All of the fasting values from the 5 subjects and 5 controls here reported are contained within the confidence bands As can be seen the prediction of the duration of ejection in the postprandial state differs in a consistent manner from the measured duration of ejection This consistent deviation of the predicted duration of ejection from the measured duration of ejection is significant at the 0.01 level of probability as deter

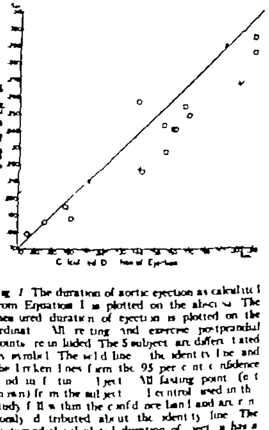


Fig 1 The duration of aortic ejection as calculated from Equation 1 is plotted on the abscissa The measured duration of ejection is plotted on the ordinate All resting and exercise postprandial points are included The 5 subjects are differentiated by symbol The solid line is the identity line and the broken lines form the 95 per cent confidence band in fasting subjects All fasting points (not shown) from the subjects and controls used in this study fall within the confidence band and are randomly distributed about the identity line The postprandial calculated duration of ejection has a significant tendency to be longer than the measurement as shown in the figure

mined by the Wilcoxon signed rank test. Thus hemodynamics in the postprandial state are altered in such a way that the period of ejection is shorter than could be predicted from the stroke index heart rate and blood pressure. If in experimental animals other parameters are held constant a short ejection period may result from an increase in myocardial contractility as has been discussed. Direct measurement of blood catechols in the postabsorptive state might provide additional insight into this problem.

In addition to the purely hemodynamic alterations found postprandially there was a significant change in the lactate pyruvate ratio. This indicates some change in the transport of oxygen postprandially. It has been suggested in previous studies that hyperlipemia after meals may result in interference with oxygen transport.[6] This would appear to be at a capillary level. Regan using the nitrous-oxide method of estimating myocardial blood flow found a decrease in myocardial oxygen uptake in some subjects after a high fat meal without appropriate hemodynamic alteration. The change occurred maximally about 3 hours after a meal. Since these changes were not apparent immediately this mechanism would not account for any changes that occurred within an hour after eating. However the increase in the lactate pyruvate ratio postprandially does suggest an increase in anaerobic metabolism compatible with some interference with tissue oxygenation. Although the present study does not allow further analysis of these alterations it is possible that alimentation results in an altered distribution of the cardiac output leading to a decreased flow to active muscle tissue. Such a mechanism has been proposed by Holmgren and associates to explain the exaggerated increase in the lactate pyruvate ratio during exercise of certain patients having abnormally high cardiac outputs during exercise.

In conclusion the data from this study suggest three alterations in hemodynamics after a meal. The first of these is a faster heart rate consistent with a decrease in effective blood volume. The second is an adrenaline-like effect or increase in the inotropic state. The third is a change in the lactate pyruvate ratio consistent with interference with oxygen transport. All of these mechanisms would tend to lead to myocardial anoxia in a patient with angina pectoris.

Summary

The circulatory and ventilatory responses to postprandial exercise were studied in normal men and compared with the fasting responses. The findings were as follows: (1) Exercising cardiac output was not affected by the meal. (2) The heart rate was faster during postprandial exercise. (3) The duration of systolic ejection was decreased out of proportion to the faster rate after the meal. (4) No significant change in arterial pO_2, pH or O_2 uptake was found in postprandial exercise when compared with fasting exercise. (5) The lactate pyruvate ratio was significantly increased during exercise after a meal.

It is concluded that the changes found can be best explained by a postprandial decrease in effective blood volume, an increase in myocardial inotropic state, and an alteration in the distribution of cardiac output.

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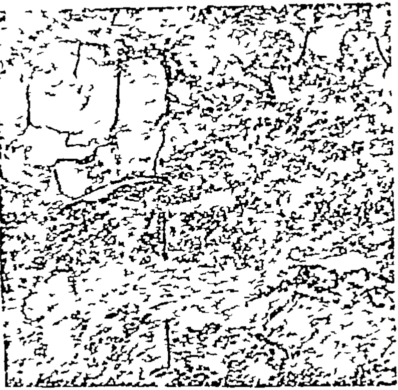


Fig. 3. Microscopic picture of the pericarditis. Area between the arrows is the lightly stained degenerated muscles in the deep epicardium. Hematoxylin and eosin. ×45.



Fig. 4. Foci of fibrosis in the myocardium. They are stellate and microscopic in size. Arrow indicates an artery with thickened wall and narrowed lumen. Hematoxylin and eosin. ×[illegible]0.

Table I

Case	Source and year	Sex, Age	Duration of [illegible]	[illegible]	Pericardial effusion	Cardiac tamponade	Associated cardiac disease
1	Sturk 1955	M		—		—	Cardiac hypertrophy—cause unknown
2	[illegible] 1946	M, 48	[illegible]			—	Hypertensive cardiac hypertrophy
3	M[illegible] 1951	M, [illegible]	[illegible]		Sanguineous 150 c.c.	+	—
4	[illegible] 19[illegible]	F, 40	[illegible]	—	Serosanguineous 500 c.c.	+	—
5	[illegible] 19[illegible]6	M	[illegible]k		Sanguineous 1,000 c.c.	+	—
6	G[illegible] 19[illegible]	F, [illegible]	[illegible]		Sanguineous [illegible]00 c.c.	+	—
7	J[illegible] 19[illegible]	M, 4[illegible]	[illegible]k	—		—	[illegible] coronary sclerosis, old myocardial scar
8	C[illegible] 1958	M, [illegible]	[illegible]	—		—	Aortic stenosis, myocardial hypertrophy, BBB
9	S[illegible] 19[illegible]	M, [illegible]	[illegible]		Sanguineous 600 c.c.	+	—
10	S[illegible]n 1960	M, [illegible]	[illegible]	+	Sanguineous small amount	—	Coronary atherosclerosis, thrombosis with [illegible]
11	K[illegible] 196[illegible]	M, adult	14 days	—	Sanguineous amount not stated	*	*
12	Present report	F, [illegible]	[illegible]	+		—	Coronary sclerosis, myocardial fibrosis, BBB

[illegible]
[illegible]
[illegible]

In reviewing other reported fatal cases without cardiac tamponade we had our attention drawn to the fact that nearly all were associated with underlying moderately severe cardiac disease. Therefore it is reasonable to suspect that pericarditis may increase the incidence of fatal arrhythmias in patients with any myocardial disease. Thus when acute idiopathic pericarditis occurs in a patient with some preexisting moderately severe myocardial disease the disease is no longer so benign.

Another feature of this case was the diagnostic challenge presented by an elderly patient with sudden onset of chest pain. In a younger patient acute idiopathic pericarditis would be more readily suspected. The accentuation of the pain at the onset of the disease by inspiration, cough, and bodily movement and the early finding of a pericardial friction rub[illegible] are extremely helpful in making the diagnosis. Typical electrocardiographic changes make the diagnosis simpler but they are not always present.[illegible] A preceding respiratory infection[illegible] and in our opinion normal serum enzymes are also helpful in the early diagnosis. In our case the lack of typical pain, absence of recent respiratory infection, the appearance of a complete

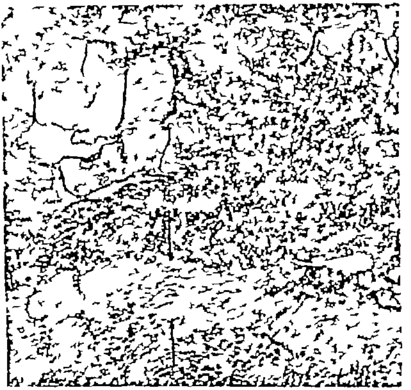


Fig 3 Microscopic picture of the pericarditis Area between the arrows is the lightly stained degenerated muscle in the deep epicardium Hematoxylin and eosin X45

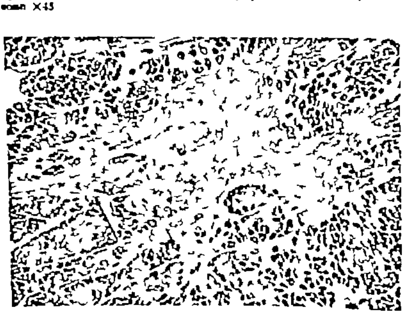


Fig 4 [illegible] of [illegible] in the myocardium They are [illegible] and [illegible] scopic in size Arrows [illegible] an artery with thickened wall and narrow lumen Hematoxylin and eosin X [illegible]0

se eral ell with replacement of young fibrous tis ue. The subepicardial myocardium lso showed loss of normal tinctorial character cytoplasmic swelli g fragmentation and loss of triation (Fig. 3). In the remaining myocardium there were many microscopic foci of fibrosis with marked intimal thickening and narrowing of the lumen of the small coronary arteries a d arterioles (Fig. 4). However, there w no ev dence indicating re ent or old myocardial infarction. Numerous histologic sections from different area of myocardium faile d to reve l n evidence of inflammation similar in n ture to that seen in the epicardium. Sections t k n through the sinu and atrio entricular nodes were al o examined. The inflammatory proce s from the epicardium impinged upon the peripher l portion of the sinus node which ppeared to be edematous (Fig. 5). In the A-V node and it surrounding structures there was r ther heavy lymphocytic infiltrate in the interstitial ti sue of the bypa t ct and the lower portion of the A-V node which the bypa tract crossed (Fig. 6). The etiol y f this isolated area of deep myocardial inflammation unclear. The left bundle branch how d marked fibrosis (Fig. 7). However the extent f pathol c lterations in these structures was not k may much as serial sect ons were not made. The inv l ement of the diaphragmatic pericardium by the fibrinous inflammatic apparentl ac ounted for the symptoms that the patient had in the upper b- domen. Microscopic studies of the kidneys revealed focal pyelonephrit and minimal hyaline thick ing in the arterioles and some of the glomerular capillary loops. The latter was interpreted as an early nephrosclerosis. The liver splee and fu showed vscu lar congestion. Mi roscopi find ng in other org ns were irrelev nt. The principal pathologic diagnosi was on pecific fibrinous pericarditis and severe coronary arteriosclerosis with focal myocardial fibrosis of an ischemic nature.

Brief review of literature

From the reported cases of acute idiopathic pericarditis with fatal outcomes (Table I) several interesting points emerge in regard to the clinical and anatomic patterns. In 5 cases cardiac tamponade was present and thought to be the cause of death. In 6 cases there was no abnormal fluid in the pericardial cavity but at necropsy the hearts exhibited other severe progressive cardiovascular diseases such as arteriosclerotic heart disease, hypertension with cardiac hypertrophy, previous myocardial infarction, aortic stenosis, and bundle branch blocks.

In the 5 cases with tamponade the fluid in the pericardial cavity was either serous or sanguinous. The administration of anticoagulants appeared to have an important role in causing hemopericardium in some instances.[1, 11] In Case 11 there was extensive inflammation of subepicardial myocardium which was believed to be responsible for death. Similar pathologic changes in the deep epicardium were observed by one other author[7] and in the present case. No mention of tamponade or other associated cardiac disease was

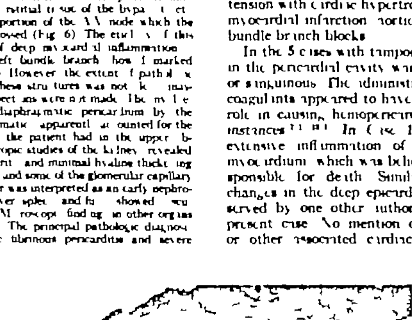


Fig. 5. The periphery of sinus node (*arrow*) and atrial muscles are involved by the pericarditis. Hem toxyl n and eosin ×2?



Fig 6 Lymphocytic infiltrate in the bypass tract (*arrow*) and its junction with the AV node (A) Hematoxylin and eosin ×45

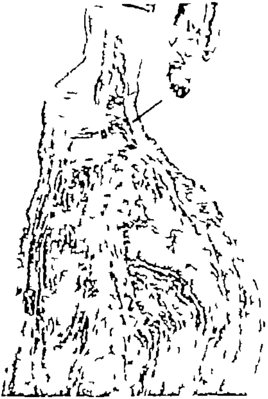


Fig 7 Fibrosis in the left bundle branch (*arrow*) Hematoxylin and eosin ×2

made by the author in Case 11 In Case 10 the patient died on the operating table during induction of anesthesia for abdominal exploration for a suspected subdiaphragmatic abscess postmortem examination showed in addition to pericarditis severe coronary atherosclerosis and recent thrombosis without myocardial infarction

Discussion

Two features of the present case merit comment first the fatal outcome in a patient with idiopathic pericarditis and second the diagnostic and therapeutic challenge that a physician has to face in some of these patients In a number of reported fatal cases of idiopathic pericarditis pericardial effusion was found and death was attributed to tamponade However in other instances there was no evidence of pericardial effusion during the clinical course and not enough fluid at necropsy to indicate tamponade The exact mode of death in the latter causes was not clear but a terminal ventricular arrhythmia or cardiac arrest was the most possible explanation Cardiac arrhythmias have been observed frequently in patients with idiopathic pericarditis [1, 17, 3] but as a rule they are transient in nature atrial in origin and should not be fatal In a clinicopathologic study of 38 cases with pericarditis and disturbances of cardiac rhythm or conduction James found involvement of the sinus node in all of them In the mechanism of cardiac arrhythmias associated with pericarditis inflammation of the following regions is important the sinus node the epicardial Purkinje tract leaving the sinus node the free wall of the atria and the epicardial nerve fibers and ganglia In our case the periphery of the sinus node and its surrounding atrial myocardium were involved by the pericarditis In addition widespread focal myocardial fibrosis and cellular infiltrate in the lower portion of the AV node and the bypass tract suggested pre existing disease possibly ischemic in nature

Table I

Case	Source and year	Sex	Age	Duration of clinical course after initial symptoms	Anticoagulant	Pericardial effusion	Cardiac tamponade	Associated cardiac diseases
1	Sturge,[a] 1885	M	7		–	—	—	Cardiac hypertrophy—cause unknown
2	Milbors, 1946	M	48	6 days	–	—	—	Hypertensive cardiac hypertrophy
3	McCord, 1951	M	57	16 days	+	Sanguinous 150 c.c.	+	—
4	Lomerance, 1952	F	46	6 days	–	Serosanguinous 500 c.c.	+	—
5	Price, 1956	M	22	3-4 wk.	–	Sanguinous 1,000 c.c.	+	—
6	Goodman,[a] 1958	F	76	14 days	+	Sanguinous 00	+	—
7	Jones, 1958	M	49	4.5 wk.	–		–	Extensive coronary sclerosis, old myocardial scar
8	Castleman, 1958	M	64	32 days	–	—	–	Aortic stenosis, myocardial hypertrophy, BBB
9	Sandison,[a] 1959	M	47	22 days	+	Sanguinous 600 c.c.	+	—
10	Swain,[a] 1960	M	19	29 days	+	Sanguinous small amount	–	Coronary atherosclerosis, thrombosis with occlusion†
11	Kimat, 1962	M	adult	14 days	–	Sanguinous amount not stated	‡	‡
12	Present report	F	69	17 days	+	–	–	Coronary sclerosis, myocardial fibrosis, BBB

[illegible]

In reviewing other reported fatal cases without cardiac tamponade we had our attention drawn to the fact that nearly all were associated with underlying moderately severe cardiac disease. Therefore it is reasonable to suspect that pericarditis may increase the incidence of fatal arrhythmias in patients with any myocardial disease. Thus when acute idiopathic pericarditis occurs in a patient with some pre-existing moderately severe myocardial disease, the disease is no longer so benign.

Another feature of this case was the diagnostic challenge presented by an elderly patient with sudden onset of chest pain. In a younger patient acute idiopathic pericarditis would be more readily suspected. The accentuation of the pain at the onset of the disease by inspiration, cough, and bodily movement and the early finding of a pericardial friction rub[1] are extremely helpful in making the diagnosis. Typical electrocardiographic changes make the diagnosis simpler, but they are not always present.[a, 3] A preceding respiratory infection[3] and in our opinion normal serum enzymes are also helpful in the early diagnosis. In our case the lack of typical pain, absence of recent respiratory infection, the appearance of a complete

bundle branch block old age and associated diabetes mellitus obscured the true nature of the active disease It was fortunate therefore that the use of anticoagulants was not complicated by pericardial hemorrhage and tamponade In doubtful situations anticoagulant therapy should be withheld

Summary

1 A fatal case of idiopathic pericarditis is reported with a brief review of the literature

2 The incidence of cardiac arrhythmias their mechanism and their possible role in the sudden death of some of these patients are discussed

3 The possible grave outcome of idiopathic pericarditis when associated with other myocardial disease is emphasized

4 The diagnostic challenge presented by this entity in older patients with associated cardiovascular diseases of varied etiology was briefly discussed

We are indebted to Dr T N James without whose guidance this report would have been impossible and to Dr W K Drake, who performed the necropsy Mr Arthur Bowden prepared the photographs

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Paradoxical acceleration of atrial flutter after "cardioversion"

Leslie J. Shalan, M.D.
Alan I. Lyon, M.D.
Bronx, N. Y.

The application of a direct-current capacitor-stored synchronized electric countershock (hereafter referred to as "cardioversion") has proved to be a valuable contribution to the management of certain cardiac arrhythmias. The use of direct rather than alternating current and the synchronization of the shock to avoid the phase of ventricular vulnerability have undoubtedly contributed to the safety and efficacy of the procedure.[1,2]

In the clinical application of cardioversion, the synchronization of the shock is such that, although the period of ventricular vulnerability is avoided, the discharge often occurs during the period of atrial vulnerability. Therefore, such a shock could conceivably initiate an atrial arrhythmia potentially more serious than the one for which cardioversion was employed. Moreover, arrhythmias such as atrial, nodal, and ventricular premature contractions, whose production is not readily explicable on the basis of a discharge occurring during the phase of atrial vulnerability, have occurred immediately after cardioversion. To our knowledge, the case reported below is the first occurrence of the unexpected acceleration of the atrial rate after cardioversion.

Case report

A 51-year-old white man with a past history of two myocardial infarctions was hospitalized because of palpitation and a rapid pulse. The electrocardiogram revealed an atrial flutter with 2:1 atrioventricular block (atrial rate of 280 per minute and ventricular rate of 140 per minute). The patient was in mild congestive heart failure, and digitalization with oral digoxin was carried out over the next 6 days. The patient lost 5 pounds in weight. The electrocardiogram revealed no change in the rhythm. After 10 days of oral anticoagulation at therapeutic level, two separate attempts to restore normal sinus rhythm with oral quinidine resulted in the production of multiple ventricular premature contractions with no effect on the atrial flutter rate or ventricular response. Quinidine was discontinued, but digitalization and anticoagulation were maintained.

Because of progressive heart failure, cardioversion was attempted utilizing a brief high-energy capacitor-stored electric shock as described by Lown and co-workers.[1] Fig. 1, taken prior to delivery of the shock, reveals persistence of the atrial flutter with 2:1 atrioventricular block. Fig. 2, taken immediately after a discharge of 100 watt-seconds, now reveals a supraventricular tachycardia with a ventricular rate of 190 per minute. Carotid compression had no effect on the rate or rhythm. The presence of an apparent initial small R wave and widening of the QRS complex with loss of the initial Q wave previously present in Lead III (see Fig. 2 *B*) strongly suggests that this arrhythmia represented an atrial flutter at a rate of 380 per minute with 2:1 atrioventricular block.

Since the tachycardia persisted unchanged for

From the Cardiac Service, Veterans Administration Hospital, Bronx, N. Y.
Received for publication June 18, 19[illegible].
*Chief Resident, Cardiac Section.
**Chief of Cardiac Section. Address: Veterans Administration Hospital, 130 West Kingsbridge Rd., Bronx, N. Y. [illegible]



Fig. 1. Lead II taken just prior to cardioversion reveals atrial flutter with 2:1 atrioventricular block (atrial rate of 280 per minute and ventricular rate of 140 per minute).

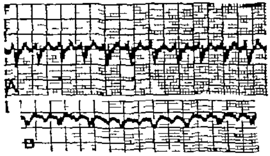


Fig. 2. A, Lead III immediately after discharge of 100 watt-second reveal atrial flutter with 2:1 atrioventricular block. However, the atrial rate is now 380 per minute. B, Lead III prior to cardioversion with atrial flutter rate of 280 per minute. Note initial Q waves not present in A.



Fig. 3. Lead II taken after discharge of 700 watt-seconds reveals sinus tachycardia at 125 per minute.

several minutes a second discharge of 700 watt-seconds was applied and was promptly followed by restoration of sinus rhythm as noted in Fig. 3 (sinus tachycardia at 125 per minute). The patient was eventually placed on a low maintenance dose of quinidine and has remained in normal sinus rhythm with no apparent sequelae.

Discussion

With the establishment of sinus rhythm by cardioversion, transient arrhythmias are frequently noted. Lown and his associates[1] analyzed the occurrence of arrhythmias during the initial 30 seconds after cardioversion of 35 episodes of atrial fibrillation. Arrhythmias were noted in 16 of the 35 patients, the most common being atrial, nodal, and ventricular premature contractions. In one patient, paroxysmal atrial tachycardia developed 10 minutes after reversion and continued to recur until full digitalization had been accomplished.

To our knowledge, this is the first case of acceleration of a pre-existent atrial flutter after cardioversion. Since the discharge was delivered during the phase of atrial vulnerability, one can speculate that the shock-induced acceleration of the atrial rate (from 280 to 380 per minute) was prefibrillatory in nature, and had the arrhythmia been allowed to persist, atrial fibrillation might have occurred. It should be added that the atrial flutter that followed the initial discharge of 100 watt-seconds was potentially a more serious arrhythmia than the one for which cardioversion was employed. Although the effectiveness and safety of cardioversion as a method of terminating certain cardiac arrhythmias has been well documented, the procedure is not without hazard.

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Traumatic rupture of the right papillary muscle in a patient with congenital atrial septal defect

*Dymitr Aleksandrow, M.D.**
Wanda Wysznacka, M.D.
Jerzy Szczerban, M.D.
Stefan Krus, M.D.
Warsaw, Poland

Reversal of flow through an atrial septal defect is known to occur as a consequence of associated malformations of the right side of the heart, increased pulmonary vascular resistance, or severe right ventricular failure. A recent clinical observation has given us the opportunity to add a further, quite unusual cause to this list.

Clinical summary

A 53-year-old man was referred to our clinic on April 23, 1964, because of intense cyanosis which had appeared suddenly about 6 weeks previously after blunt trauma to the anterior chest wall. Up to the time of the accident he had been asymptomatic and acyanotic. During all of his adult life, including the day of the accident, he had been engaged without apparent distress in heavy manual work. On March 3, while at work, he suffered a severe blow on the precordial region and collapsed. He was taken immediately to the local hospital. On admission he was in shock, although no significant external injury could be discovered. Despite recovery from the initial shock the patient's condition remained grave. He was unable to stand or sit because of severe dizziness, blurring of vision, and the feeling of impending collapse when he was in the upright position. Progressive cyanosis appeared within the first week after the accident. He was referred to us 6 weeks later with the suggestion of traumatic heart disease.

Physical examination revealed a conscious, severely disabled but cooperative man of normal body build, deeply cyanotic, lying flat in his bed without visible respiratory distress. Neither clubbing of the fingers nor edema was present. The lungs were normal to percussion and auscultation. The respiratory rate was 24 per minute. The heart appeared to be normal on palpation. The heart rate was regular, about 100 per minute. A Grade 2 short systolic murmur, not modified by respiration, was heard along the left sternal border without propagation to the axilla. On a phonographic tracing the murmur ended about 0.05 second before the aortic component of the second sound. The pulmonary component could not be clearly identified. The radial pulse was small and regular. The arterial pressure was 100/80 mm. Hg. Huge palpable venous pulsations were present in both jugular veins. On indirect record (Fig. 1) the venous pulse consisted of a single high wave of apparently ventricular shape. The filling of the jugular veins during diastole appeared to be normal. The liver and spleen were not palpable. The x-ray film of the chest revealed a moderately enlarged heart and normal pulmonary vessels. Detailed radiologic examination of the heart was difficult because the patient was unable to tolerate the upright position for more than a few minutes. The electrocardiogram (Fig. 2) revealed a normal sinus rhythm and signs suggestive of right ventricular hypertrophy with an rSr' pattern in Lead V_1. Laboratory findings were as follows: red cells 6,700,000, white cells 4,100, hemoglobin 112 per cent, urinalysis normal except for trace of albumin, arterial blood/femoral artery/O_2 saturation 67 per cent, pH 7.45, pCO_2 26 mm. Hg.

The clinical findings suggested severe tricuspid incompetence, probably of traumatic origin, combined with a large right-to-left shunt. An atrial septal defect of traumatic or congenital origin seemed to be the most probable site of the reversed shunt. Simultaneous traumatic rupture of the in-

From the Second Medical Clinic, Medical Academy, Warsaw, Poland.
Received for publication June 25, 1964.
*Second Medical Clinic, Medical Academy, Nowogrodzka 59, Warsaw, Poland.

teratrial septum and of one or more of the right papillary muscles has been reported but survival for 7 weeks with such a combined traumatic lesion seemed to be improbable. The ECG findings were compatible with the existence of a congenital atrial septal defect. Its presence was seriously taken into consideration despite the complete lack of cardiac symptoms prior to the accident. It is known that an atrial septal defect is occasionally well tolerated until late adult age.

Catheterization of the right side of the heart was performed 24 hours after admission despite the grave condition of the patient in hopes that the cardiac lesion might be amenable to surgical repair. The right atrial pressure tracing showed a deformation suggestive of severe tricuspid incompetence. The pressures recorded on the right side of the heart were unusually low: right atrium 8/? right ventricle 13/?/0 pulmonary artery 13/5 and pulmonary capillary pressure about 2 (mm. Hg).

No systolic gradient was found between the pulmonary artery and the right ventricle. Coomassie blue dye was injected successively into the main pulmonary artery, right ventricle and right atrium and estimated photometrically in centrifuged samples of blood taken from the femoral artery every 2 second. The dye appeared in the femoral artery 18 seconds after its injection into the pulmonary artery and 9 seconds after its injection into the right ventricle and right atrium. The results of cardiac catheterization were interpreted as being compatible with the diagnosis of traumatic tricuspid incompetence combined with reversed shunt through an atrial septal defect.

Unfortunately on the evening of the day of the catheterization the patient developed right hemiparesis with loss of consciousness and ophthalmic signs suggestive of the occlusion of the left internal carotid artery. He died of this complication ? d later.

Pathologic findings. Postmortem examination performed 6 hours after death in the Department of Pathological Anatomy, Medical Academy, Warsaw, revealed the following findings. The skin over the cardiac region showed slight cicatrization. The heart was of normal size. The pericardium was either covered with fibrin or showed fresh adhesions with the epicardium on the total surface of the right ventricle. The right ventricle was slightly dilated.

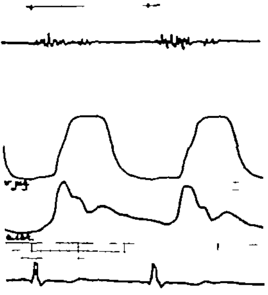


Fig. 1. *From above:* Phonocardiogram showing short systolic murmur, jugular venous pulse with waves of ventricular shape, carotid arterial pulse and electrocardiogram.

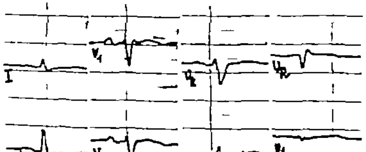


Fig. 2. Electrocardiogram showing regular sinus rhythm, ... signs of right ventricular hypertrophy.



Fig 3 The heart at postmortem examination Above Ruptured papillary muscles of the right ventricle (indicated by arrows) Below The atrial septal defect seen from the right atrium

Both ventricles contained unclotted blood The outflow tract of the right ventricle the aortic and pulmonary valves and the tricuspid valve were normal Two papillary muscles of the right ventricle were ruptured Their free ends were smooth and white (Fig 3 above) Under the endocardium of the anterior wall of the right ventricle a white plaque was visible The myocardium of both ventricles and the intima of the aorta pulmonary artery and coronary arteries appeared to be normal The interventricular septum was intact The interatrial septum contained a circular defect that was about 2 cm in diameter (Fig 3 below) No signs of traumatic injury to the interatrial septum were present

The spleen (190 grams) kidneys (140 grams each) and liver (1 (30 grams) showed passive congestion The right kidney showed a fresh anemic infarction Fresh obliterating thrombus was found in the right ... and hepatic vein The left ... artery and the left median artery of the brain were filled with fresh ... thrombus The white matter and basal ganglia of the left cerebral hemisphere and the left part of the pons showed ...

The final pathol... diagnosis was rupture of two papillary muscles of the tricuspid valve ... fibrosis of the anterior wall of the right ventricle ... atrial septal defect of the secundum type fibrinous and adhesive pericarditis ... fresh thrombosis of the right brachial vein and hepatic vein fresh thrombosis of the left ... artery and left median artery of the brain softening of the white matter ... of the left cerebral hemisphere and of the left part of the pons ... anemic infarct of the right kidney

Discussion

Rupture of papillary muscles is a relatively rare cardiac lesion Most reported cases occurred as a complication of a recent myocardial infarction involved the left ventricle and led quickly to death because of resulting severe mitral incompetence Recently attempts at surgical repair of this lesion have been reported[4]

Traumatic etiology of the rupture of papillary muscles is less common at least in clinical reports Only 6 cases of traumatic etiology are cited among 61 cases of rupture of the papillary muscles reviewed by Sanders and associates[4] No mention of this lesion could be found in several reviews of clinical consequences of blunt heart trauma Rupture of papillary muscles is however a recognized pathologic consequence of nonpenetrating heart trauma It was found 24 times among 546 autopsy cases of nonpenetrating traumatic injury to the heart reported by Parmley and associates[1] In all but 3 cases in their series rupture of papillary muscles was associated with other immediately fatal lesions The only patient who survived the initial injury by more than a few hours was a man with isolated traumatic rupture

of the right anterior papillary muscles. He survived in a relatively good condition for 4 months after the accident and died when surgical repair of the heart lesion was attempted. To our knowledge it is the only reported case of clinically diagnosed traumatic rupture of the right papillary muscles.

A comparison of the description of that case with the clinical findings in our case reveals a number of common features which form a quite distinct clinical picture. Both patients suffered severe trauma to the chest followed by reversible shock and the subsequent appearance of peripheral signs of gross tricuspid incompetence. They had a regular rhythm and little or no enlargement of the heart—a finding seldom encountered in the presence of tricuspid regurgitation of more common etiology. In both patients there was a systolic murmur of moderate intensity and without palpable thrill. It seems noteworthy that the lack of a thrill has been stressed repeatedly in clinical descriptions of rupture of the left papillary muscles[3,4] and is considered to be a useful sign in the differential diagnosis between this lesion and a ruptured interventricular septum. A right atrial pressure tracing showed marked ventricularization in both subjects. Normal or low pressures were recorded from the right ventricle and the pulmonary artery. Although the final outcome was fatal in both cases, the lesion was far better tolerated than rupture of the left papillary muscles and allowed a survival of several weeks after the injury.

Rupture of the left papillary muscles is usually quickly fatal because of intractable pulmonary edema. Rupture of the right papillary muscles creates a less dramatic situation since the regurgitant flow of the right ventricle can be accepted by the systemic veins without immediate detrimental effect. The clinical picture and available hemodynamic data in our case suggested circulatory failure of a predominantly forward type with normal venous and right ventricular end-diastolic pressures, markedly prolonged circulation time, low pulmonary and systemic pressures, and symptoms of inadequate cerebral blood flow. This suggest that the circulatory failure was caused by purely mechanical factors rather than by failure of the cardiac muscle. The injured right ventricle was able to empty normally during systole but a large part of its output was wrongly directed.

The clinical observation that only the prone position could be tolerated by the patient may probably be explained by the fact that this position helped to increase the effective right ventricular output because of increased venous return.

Severe circulatory failure probably contributed —together with polycythemia secondary to the reversed shunt—to the extensive vascular thrombosis that was directly responsible for the fatal outcome. Extensive phlebothrombosis was found at autopsy not only in the brachial vein used for catheterization but also in hepatic veins which were not entered during the procedure. Very probably the final cerebral thrombosis was initiated by a paradoxical embolus that originated from thrombosed systemic veins.

A combination of the traumatic lesion of the papillary muscles with the preexisting atrial septal defect was responsible for the peculiar appearance of central cyanosis after the trauma to the heart. This combination might have been purely accidental. It seems possible, however, that prolonged exposure of the patient's right ventricle to a considerable volume load might have been a factor predisposing to injury.

Summary

Traumatic rupture of two right papillary muscles in a man with a congenital atrial septal defect resulted in a reversal of flow through the defect with the sudden appearance of central cyanosis and caused severe circulatory failure of a predominantly forward type. The patient survived for [illegible] weeks after the injury and died from thromboembolic complication shortly after cardiac catheterization.

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Acid base balance

A review of current approaches and techniques

*William H Austin M.D.**
Portland Me

Approaches to acid base balance

Until 1948 when Singer and Hastings[1] published their nomograph describing the concept of buffer base acid base problems were interpreted within the framework of the Henderson Hasselbalch equation which describes the relation between pH pCO_2 (or H_2CO_3) and bicarbonate. Buffer base added a new parameter designed to separate the respiratory and nonrespiratory (metabolic) changes and was originally defined as "the base equivalent to the sum of buffer anion concentration (including HCO_3^-) in milliequivalents per liter." The physiologic basis for this concept is the fact that changes in carbonic acid are buffered by protein anion. In respiratory defects any increase or decrease in the bicarbonate is initially accompanied by an equal and opposite change in the protein anion existing in the basic form leaving the buffer base unchanged. When changes in the buffer base occur a metabolic component is judged to be present. If in respiratory acidosis an increase in the bicarbonate concentration occurs which is greater than can be accounted for by a decrease in protein anion buffer base is increased beyond the normal range and a metabolic alkalosis primary or secondary is diagnosed. Likewise in respiratory alkalosis when the bicarbonate decrease is greater than can be accounted for by an increase in protein anion a coexisting primary or secondary metabolic acidosis is present. This approach attempts to make a clear-cut distinction between those changes in bicarbonate which are due to and balanced by a change in the protein anion concentration and those changes which are secondary to metabolic factors of primary or secondary origin. The biochemical data give no information about the nature of the metabolic component whether it is the anticipated secondary change or a coexisting superimposed primary defect. In the primary metabolic disorders the diagnosis of pure or mixed disturbance is based on the presence or absence of a normal pCO_2. In the case of metabolic acidosis when the anticipated hyperventilation and decrease in pCO_2 occurs metabolic acidosis with secondary respiratory alkalosis is present according to the Singer Hastings system. So called pure metabolic acidosis is said to exist with a decrease in bicarbonate and buffer base but with a normal pCO_2. As will be pointed out later such a situation probably represents metabolic acidosis with superimposed respiratory insufficiency of a relative degree. The reverse situation is generally true for metabolic alkalosis. However we agree that a normal pCO_2 is often seen with an elevated bicarbonate and from the physiologic viewpoint such a situation does probably represent pure metabolic alkalosis.

In recent years there has been a revival of interest in the buffer base concept in

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*Director, Section of Renal Physiology, Cardiovascular Department, Maine Medical Center, Portland, Me. [illegible]

the form of the Astrup approach and the Siggaard Andersen nomogram.[8] In addition to buffer base, two new parameters, standard bicarbonate* and base excess† have been introduced. These two entities are also used as an index of nonrespiratory or metabolic changes. In the Siggaard Andersen curve nomogram, buffer base, standard bicarbonate, and base excess are superimposed on a pH-pCO₂ plot. The construction and use of this graph is described elsewhere.

The validity of both these approaches has been challenged by Schwartz and Relman[9] on conceptual and physiologic grounds. They suggest that parameters such as base excess may add confusion rather than clarity to the therapeutic considerations. The finding of a positive base excess or increased standard bicarbonate does not necessarily indicate the need for measures to reverse these values to normal, since they may reflect the usual compensatory changes. They further question the validity of standard bicarbonate in vivo and in vitro. The lack of correlation was subsequently documented[10, 11] in dogs and human beings by determining the bicarbonate concentration of a sample of blood exposed to a given pCO₂ and the concentration actually present when the subject was exposed to the same partial pressure of carbon dioxide. Actually, similar studies were made by Siggaard Andersen,[8] but the difference between in vivo and in vitro results was not thought to be of clinical significance.

From Schwartz's studies it appears that part of the bicarbonate generated from whole blood buffers in respiratory acidosis diffuses into the interstitial space. This may in part account for the "metabolic acidosis" which is said to exist in acute respiratory acidosis as diagnosed using the Singer-Hastings approach.[1] It seems somewhat arbitrary to make a distinction between changes in bicarbonate which result from whole blood buffers and those occurring secondary to ion transfer, changes in organic acid level, and renal factors.[12, 13] Both types of changes may be compensatory in nature. They are in a sense metabolic since they involve a change in bicarbonate, yet at the same time are secondary to changes in alveolar ventilation. The systems described above afford no distinction between superimposed primary and secondary metabolic defects, and a certain amount of confusion is produced by calling a primary respiratory disturbance with its expected metabolic compensation a "mixed defect." We have reserved the use of this term for two primary coexisting defects and consider a defect pure when the primary disturbance is associated with the usual or expected degree of compensation.

A third and relatively unheralded approach is that one advocated by Poppell and associates[4] and Roberts and associates.[1] These investigators, employing the classic parameters of pH, pCO₂, and CO_2 content, attempted to define the magnitude of changes encountered in various acid-base disorders. For this they employ a pCO₂-CO₂ content plot which they found to be most convenient to represent the changes. They studied the magnitude of ventilatory change in metabolic disorders in patients with normal and abnormal pulmonary function. They likewise made observations of the bicarbonate alterations in primary pulmonary disorders without associated metabolic disease. From this information they were able to determine the *expected* or *usual* degree of compensatory change in various primary defects. This also allowed the detection of superimposed problems which, with the use of the broader definitions, would go unnoticed (e.g., metabolic acidosis and pulmonary insufficiency). We combined their observations with over 400 of our own and included some important additions by Robin.[2] The findings are expressed graphically in Fig. 1, which delineates the various patterns referred to earlier. Here pCO₂ and $BHCO_3$,‡ two components of the Hender-

*The standard bicarbonate equals the CO_2 content of plasma separated from whole blood equilibrated with pCO_2 of 40 mm. Hg at 38° C.

†The base excess is defined as titratable base, titrated to normal pH at normal pCO_2 and normal temperature, calculated as a deviation of standard bicarbonate times 1. [illegible]

‡Poppell [illegible] pCO₂ and CO_2 content [illegible] bicarbonate [illegible] [illegible]

son Hasselbalch equation are put into apposition. The use of pCO and bicarbonate makes a linear plot and it is convenient to think of these two parameters as representing respiratory and metabolic factors respectively. Fig 1, the pCO/bicarbonate plot modified from Poppell* and associates, is based on the blood measurements described later. The expected range of values for metabolic acidosis, respiratory alkalosis, metabolic alkalosis and respiratory acidosis is appropriately labeled. Mixed defect 1 results when chronic or acute ventilatory insufficiency (relative or absolute respiratory acidosis) is superimposed on a defect producing a low bicarbonate value (i.e. metabolic acidosis or respiratory alkalosis). Mixed defect 2 is present when ventilatory insufficiency is superimposed on metabolic alkalosis and an identical picture may be present in respiratory acidosis when there is a decrease in pCO_2 without a simultaneous fall in the bicarbonate. This sustained elevation of bicarbonate may be secondary to depletion of chloride and replacement of chloride will restore the picture to one of respiratory acidosis. Loss of chloride through vomiting in a patient with respiratory acidosis will also produce this mixed defect. Some investigators[3] found that the administration of bicarbonate produced metabolic alkalosis with an elevated pCO (mixed defect 2) but this is not a common finding in our experience. 4 is an indeterminate area. Points following this region could represent one of several possibilities, however precise characterization is not always possible on biochemical grounds. The line separating respiratory acidosis and mixed defect 2 is not an exact boundary between the two regions and interpretation in this area as always should be tempered by the clinical situation. In general acute changes fall in the left half of the respiratory acidosis area and the more chronic changes in the right. Plots of pH/log pCO and pH bicarbonate could be used to express the same information, however we believe that the clinician gains greater insight into the dynamics of the acid base situation and is able to transpose the laboratory finding to the clinical situation more easily with a pCO / $BHCO_3$* plot. The pH although useful and necessary is not specifically made part of the diagram presented here mainly for reasons of simplicity.

The following features are worthy of note. Although implied some of these facts are not readily apparent from inspection of the graph.

1 Metabolic acidosis rarely exists as a compensated defect when the $BHCO_3$ is below 16 to 18 mM per liter and is increasingly uncompensated below this value. Even in the absence of pulmonary disease with bicarbonate levels above 16 to 18 mM per liter the acidosis is frequently compensated (pH above 7 36).

2 Metabolic acidosis usually exists as an uncompensated defect in the presence of chronic pulmonary disease at all values for $BHCO_3$ (mixed defect 1).

3 Respiratory alkalosis usually exists with a variable pH ranging from normal to high. Below 16 mM per liter the pH tend to be more nearly normal. The range of expected pCO values is much wider than in uncomplicated metabolic acidosis. Respiratory alkalosis rarely exists alone with a $BHCO_3$ below 13 mM per liter.

4 Primary respiratory alkalosis and metabolic acidosis coexisting as primary defects cannot be diagnosed accurately but can be suspected when a moderately low BHCO exists with a near normal pH.

5 Metabolic alkalosis unassociated with primary pulmonary disease is characterized by a high bicarbonate and a normal or only slightly elevated pCO *. (One investigator reported elevated pCO in patients receiving bicarbonate but recalculated pCO s from his pH and bicarbonate

*Some [illegible] object to the use of $[BHCO_3]$ instead of $[HCO_3]$ however it should be remembered that $[BHCO_3]$ [illegible] the activity coefficient (γ) which [illegible] practice [illegible] are the working [illegible] constant [illegible] $[HCO_3]$ $[BHCO_3]$ ×

$$\gamma = [HCO_3] \quad [H^+] = \frac{H_2CO_3}{[HCO_3]} Ka \qquad [H^+] = \frac{H_2CO_3}{[BHCO_3]} Ka$$

$$\text{Since } Ka/\gamma = K \text{ then } [H^+] = \frac{H_2CO_3}{[BHCO_3]} K \text{ (Ka and K [illegible]}$$

the true [illegible] apparent [illegible] constant respectively.) The [illegible] log of the apparent [illegible] K has been [illegible] pK for the [illegible] and other [illegible] HCO_3 [illegible] [illegible] [illegible] bicarbonate [illegible] although others have employed the notation for bicarbonate concentration. The [illegible] of $[HCO_3]$ [illegible] for the use of $[BHCO_3]$ for bicarbonate concentration.)

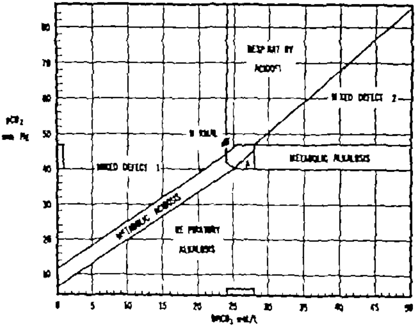


Fig. 1. pCO/BHCO plot for venous blood. *Mixed defect 1*: Metabolic acidosis with ventilatory insufficiency. *Mixed defect 2*: Metabolic alkalosis with ventilatory insufficiency or improving respiratory acidosis with sustained elevation of BHCO. A is an indeterminate area. See text.

values failed to reveal any elevation of pCO (above 45 mm) during the time the subjects were breathing room air.)

6. Metabolic alkalosis associated with severe depletion of potassium, some degree of primary pulmonary disease or improving pulmonary disease without adequate replacement of chloride may give the picture of an elevated bicarbonate and moderately elevated pCO with alkaline to normal pH (mixed defect 2).

7. Chronic respiratory acidosis is associated with an elevated pCO_2 and $BHCO_3$ and a normal to markedly lowered pH. The diagnosis of a superimposed metabolic acidosis without an absolute decrease in bicarbonate (below 24 mM per liter) is difficult to make with the current information but may be suspected when values fall in the left half of the respiratory acidosis area.[10,11]

This device is only a guide and too much reliance should not be placed on it. The bar for metabolic acidosis represents two standard deviations in our hands but other areas are not so well defined at the present time. Various situations may produce misleading plots, for instance the combination of vomiting and diarrhea may result in a normal picture in the face of marked depletion of chloride and bicarbonate. Such a device, however, is helpful as a summary of the natural patterns of acid base disorders and thus is an aid to diagnosis and treatment. The absolute validity of the figures presented here may be questioned by some but the approach represents a clinical corollary rather than a biochemical preoccupation. Acid base problems are troublesome enough for those who deal with them regularly and are more of a problem for the clinician who sees them only occasionally. For this reason a few familiar parameters, provided that they adequately define the situation, seem to be preferable to a multitude of less tangible ones, particularly if they only add needless confusion.

The blood sample

The choice of which type of blood sample to use for routine determinations has been hotly debated.[1,3] Arterial blood is most desirable but more difficult to obtain when frequent measurements are desired. This is not a serious drawback but if either venous or capillary blood gives the same

information sampling would be simplified Wide variations between arterial and venous pH and pCO_2 have been reported[34] and are said to be related to oxygen saturation cardiac output and high pH values Gambino[8 19] found less variation between plasma values and a wide scatter with whole blood He apparently used fluoride in some samples which may have unpredictably affected the pH values[18] Brooks and Wynn[37] report that venous blood taken from the dorsum of the unheated hand gives results similar to those with arterial blood It is not always feasible to sample in this manner particularly without stasis Capillary blood when it can be obtained with relative ease gives values very close to arterial samples[33 1 14] Large errors occasionally may be made unwittingly especially when the operator is not thoroughly experienced with microtechniques necessary for capillary samples We find as did Poppell and associates[34] less variation in pH and pCO_2 when the venous blood is drawn without stasis or pumping of the hand Normal values for pCO calculated from pH and pCO_2 content range from 40 to 47 mm Hg We hasten to add that this finding is at variance with that of others who note a greater range and difference in the pCO_2 It should be noted that venous pCO determined by the Astrup equilibration technique will yield a low pCO when the pH of the unsaturated venous sample is put into the pH/pCO_2 plot[32] This could be predicted from the work of Peters and Van Slyke[4] and is related to the fact that oxygenated blood has a lower pH than reduced blood at the same pCO_2 The absolute difference between arterial and venous blood is of little importance provided that the findings in various defects fall into consistent patterns Like that of Poppell and Roberts our experience with venous blood has shown this to be the case Fig 1 is based on venous samples drawn in the manner described but a similar system for arterial blood is perfectly feasible and perhaps even more desirable The patterns found with arterial blood have not been worked out in detail but they are apparently fairly similar to those found with venous blood[34]

Once the sample is obtained if it is stored in ice little change in pH or CO content will occur for about 1 hour[33] Unpublished work indicates that at room temperature the pH changes by 0004 pH units per minute and at 37 or 38°C the changes are of the order of 001 per minute Severinghaus[34] and Siggaard Andersen[36] found that plasma pH is higher than whole blood pH by approximately 01 units and some workers have routinely added this value to whole blood pH Gambino could not find any consistent difference between whole blood and plasma[36] His work is difficult to evaluate not only because fluoride was used but because of instrumentation The inherent error of his pH meter alone exceeds the difference in whole blood and plasma pH reported by some observers[31 36] Salenius findings of a 048 difference is subject to some question[37] If the temperature separation does have an effect on the pH in the manner described by Rosenthal[3] then Salenius results could be due to separation of plasma at temperatures below 37 or 38 C We re evaluated this problem in the manner described by Severinghaus[34] but used a shorter centrifugation time (less than 5 minutes) Our differences were slightly greater than 01 pH units between plasma and whole blood The slightly higher values are undoubtedly due to the use of a liquid junction which was not thermostated The observed pH difference between whole blood and plasma is apparently due to a change in the liquid junction potentials created by the use of concentrated KCl since the difference is obliterated with isotonic saline bridges[39] The temperature of the liquid junction as previously referred to has a very definite effect on the pH decreasing the value by 001 units for every degree centigrade below 38°[3] Despite some evidence to the contrary we think that whole blood should be used for pH measurements and 01 added to the observed value Separating plasma at 37 or 38°C for pH measurement is inconvenient and does not really improve the accuracy Glycolysis which takes place during separation over a 20 minute period results in a decrease in plasma pH equal to or exceeding the difference between whole blood and plasma

Fortunately the CO content is not significantly altered by the temperat

separation.[22,24] Centrifuging samples for CO_2 content under mineral oil does not result in significant loss of CO_2 as is often stated.[4] In 20 paired samples, one set spun in a syringe, the other under oil in the routine fashion, the average difference in CO_2 content was 0.2 mM per liter with the greatest being 0.9 mM per liter.

Buffers and pH measuring systems

Two buffers in the physiologic range (6.840 and 7.387) are by far the most useful for calibrating a pH measuring system for physiologic work. The buffer salts (phosphate) are prepared by the National Bureau of Standards. The value cited above for the 7 buffer is slightly higher than that given by the National Bureau of Standards because of the presence of liquid junction potentials encountered with clinical electrodes.[1] These buffers are not difficult to make, are more reliable than most of those commercially available, and are less expensive. They may be used to calibrate buffers which are made with less precision. The higher buffer is slightly less stable than the 6.8 buffer, and its deterioration may be detected by a decrease in the pH difference between the two.

At present there are on the market a number of excellent pH meters that have a high degree of accuracy. The EMF/pH ratio of the pH meter may be checked with the potentiometer (61.64 mv. per pH at 37.5° C.) to be sure that the response of the instrument is appropriate. However, this is usually unnecessary with the better instruments. The over-all response of the electrometer and the electrode taken as a unit is actually the more important factor. The electromotive efficiency of the electrode may deviate from the theoretical value, but any significant variation in electrode output may be detected by the use of the two buffers described. If the output of the electrode is low, the slope control or the temperature control (which controls the millivolts required to give a certain pH value) may be adjusted until the two buffers agree. Deviations in electromotive efficiency should not be confused with buffer inaccuracy. This can be checked by making new batches of buffer. Once a system's response has been appropriately set, the 7.387 buffer alone may be used to standardize the equipment, provided that periodic checks are made against the lower buffer. Highly alkaline buffers have little place in physiologic systems because of the alkaline error of most glass electrodes. Acid buffers, such as phthalate, are less objectionable, but their distance from the pH being measured may introduce an error not seen with the use of buffers nearer the pH of blood. These acid buffers are of value in calculating the system over a greater span. Semple and associates[a] have described a 7.416 phosphate buffer with an ionic strength similar to that of blood (13). This buffer has no great advantage over the buffers of the National Bureau of Standards. Bates has described several reasons for using buffers with an ionic strength below 1, and the reader is referred to his excellent book on pH measurements for further details.[4]

For best results, thermostated reference electrodes and liquid junctions should be employed, as well as temperature control of the glass electrode. As referred to earlier, the use of a liquid junction at room temperature[3] will yield plasma pH values .015 higher than those with junctions controlled at 37 or 38°C. We have been able to confirm the existence of this phenomenon in whole blood and suggest that thermostated junctions be adopted to better standardize pH results.

The use of pCO_2 electrodes such as those described by Severinghaus[a] has gained wide acceptance. They have the advantage of giving rapid results without the need for separating the blood. Those who prefer pH/pCO_2 plots will find this technique particularly suitable, since calculations are eliminated and the bothersome problem of pK is obviated. Values of pCO_2 obtained with the electrode agree well with other direct measurements of pCO_2.

The Astrup microtonometer technique of determining pCO_2 by equilibrating blood with two gases of known pCO_2 is simple and rapid.[5] As alluded to earlier, if the original sample is unsaturated, falsely low pCO_2's will result. In most situations this would not be a problem, provided that either arterial or capillary blood was used. This system has the same general advantages of the pCO_2 electrode in the

[illegible] may be obtained from the National Bureau of Standards, Washington, D. C. [illegible] with instructions for preparation of the two buffers referred to above.

rapidity with which the answers can be obtained

Calculation of conversion tables and pKs

Experimental pK for the carbonic acid buffer system in plasma differs considerably from the true pK for carbonic acid. The apparent pK is a composite of the first dissociation constant of carbonic acid, the activity coefficient for bicarbonate and a factor which permits dissolved carbon dioxide to be treated as carbonic acid. In addition, the temperature, pH, and solubility coefficient have a real or apparent effect on the pK. The solubility coefficient of CO_2 is itself a function of temperature, electrolyte, protein, lipid and water content of plasma. There is little wonder that there has been disagreement in published values for pK. One author suggests that each individual determine his own pK.[42] Several objections could be raised to this. One of these is that several variables and sources of error are inherent in the procedure itself. Variations from laboratory to laboratory would most likely represent technical errors in equilibration and sample handling rather than true differences in the pK, even though determinations of pH and carbon dioxide content may be made with a high degree of accuracy.[43,44,45] Therefore, it seems reasonable to adopt pK at 37.5 C adjusted for pH using the appropriate solubility coefficient for CO_2. The value may be arbitrarily chosen or based on current experimental data. The latter is the logical approach. The choice of 37.5°C has physiologic significance, although if a given investigator chooses to use 37 or 38 C, he can still employ pK for 37.5°C without significantly altering the calculations.

The whole problem may be considerably simplified by using a nomogram or set of tables (incorporating appropriate pK's) for making calculations in lieu of solving the Henderson Hasselbalch equation. A nomogram employing a fixed pK, such as that of Singer and Hastings,[1] is preferred by some. The nomogram is somewhat cumbersome to use and is subject to small inaccuracies.

The alternative to a nomogram has been suggested by Milch, Bane and Roberts.[46] From the rearranged Henderson Hasselbalch equation a pCO factor may be determined for various pHs. This factor is given by the term [1+ antilog (pH−pK)] S, where S* is the solubility factor calculated as follows: S = α†/ 76 22.26. The pCO_2 factor may be divided into the CO content to yield pCO_2. With the advent of the pCO_2 electrode some investigators and clinicians find it easier to determine pH and pCO. In order to arrive at a figure for bicarbonate from a determined (or calculated) pCO, we have calculated a second set of factors given by the expression [1+ antilog (pH − pK)] S − S. These bicarbonate factors may be multiplied by the pCO to yield bicarbonate. From such a set of factors pCO_2 and $BHCO_3$ may be calculated with ease. The method of calculating pCO_2 and bicarbonate is presented in the footnotes to Table I. As alluded to earlier, preparation of a set of factors poses a major problem in respect to the choice of pK. The best modern experimental data, although limited, are those determined by Siggaard Andersen[45] using highly accurate buffers and pH measuring systems. He found the pK at 7.4 and 38 to be 6.104. Severinghaus[44] noted a change in the pK with temperature of approximately −.006 pH units per degree centigrade. Austin, Lacombe, Rand and Chatterjee[47] recently determined the solubility factors for CO_2 in human serum with known water content (.935 grams per milliliter at 23 C) and found slightly higher values than those used by Siggaard Andersen. If his work is corrected for temperature and a slightly different solubility coefficient, the pK becomes 6.11 at 37.5°C and 7.40.

The apparent change in pK with pH (possibly due to the presence of carbonate[48]) is well known. Through the physiologic range it may be considered to be linear. The pK pH regression coefficient is −.047,[46] but a value of −.05 may be used without introducing any significant error. Actually this means a variation of only .04 in the pK throughout the range of 6.9 to 7. From the foregoing information pK's for various pHs have been determined and have been used in the calcu

* = H CO_2 (mM L)/pCO_2 (m Hg)
† = Sol bility coeffic[illegible] ml CO_2/ml pl m

Table I Conversion factors for calculation of pCO_2 and $BHCO_3$ at 37 5°C *

pH	pCO † factor	BHCO factor	pH	pCO factor	BHCO factor	pH	pCO factor	BHCO factor
6 90	20	1 7	20	396	36	50	85	755
1	211	181	1	404	374	1	803	773
2	216	186		413	383	2	821	791
3	20	190	3	4 2	392	3	839	809
4	224	194	4	433	403	4	858	828
5	229	199	5	443	413	5	87	84
6	235	205	6	455	425	6	90	867
	241	211	7	465	435	7	927	89
8	246	216	8	475	445	8	948	918
9	250	20	9	485	455	9	969	939
00	56	226	30	496	466	7 60	992	962
1	261	231	1	507	47	1	1 01	984
2	266	236	2	518	488	2	1 03	1 00
3	27	242	3	529	499	3	1 06	1 03
4	27	24	4	541	511	4	1 08	1 05
5	284	254	5	553	523	5	1 11	1 08
6	29	262	6	571	41	6	1 14	1 11
7	298	268	7	583	553		1 17	1 14
8	304	2 4	8	596	566	8	1 20	1 17
9	312	282	9	609	5	9	1 23	1 20
10	318	287	7 40	6 3	593	70	1 25	1 22
1	324	294	1	63	607	1	1 28	1 25
2	331	301	2	631	621	2	1 31	1 8
3	338	308	3	665	635	3	1 34	1 31
4	345	315	4	680	650	4	1 37	1 34
5	55	322	5	696	666	5	1 40	1 37
6	364	334	6	714	683	6	1 44	1 41
7	3 1	341	7	731	01	7	1 48	1 45
8	3	342	8	49	712	8	1 5	1 49
9	35	35	9	67	37	9	1 56	1 55

*† ... 6 11 ... H ... 05 ... factor = 0304 temperature = 37 5 C (37 38 C)

$pCO_2 = \frac{CO_2\ content}{pCO_2\ factor}$

$BHCO_3 = pCO_2 \times BHCO_3$ factor

lation of the pCO and bicarbonate factors shown in Table I

If consideration is given to all the variables mentioned pH should be accurate to the nearest 005 CO to + or − 25 mM and pCO to the closest millimeter of mercury Being able to report results to this degree of accuracy is not of importance in itself However using buffers and equipment with a high degree of accuracy and reliability eliminates one possible source of inaccuracy which if added to causes of error such as those inherent in sampling would become significant

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Fundamental considerations on blood volume

Physiologic and clinical aspects

Hans Scholer, M.D.
Liestal, Switzerland

It is possible today in the hospital to determine rapidly, exactly, on repeated occasions, and without danger to the patient the volume of the blood, or rather the volume-capacity of the vessels, or even more precisely the volumetric distribution at a given time of a γ isotope (I^{131}) firmly bound to human albumin. The measurements obtained in this way in the hospital are most valuable. However, if actual interpretations and not just longitudinal comparisons are required—and this is obviously desirable—considerable difficulties arise. Then one inevitably has to fall back on seemingly remote and unrelated facts.

Blood volume in animal species

In searching in the animal kingdom for relationships between blood volume and structural and functional characteristics, one must aim to establish whether the total volume of the blood vessels is related to the total performance for which the organism is constructed. This can in fact be shown. For a given genus there is a clear correlation between the weight of the heart and the oxygen transport stroke volume on the one hand, and the blood volume, total hemoglobin content and body weight on the other when plotted on a double logarithmic scale. There is also a rough but striking relationship with performance indices. This is true of course only for organisms in which a closed circulation guarantees economical vascularization. Fig. 1 shows good correlations in mammalians.

If we approach the problem in greater detail, the relationship to motor performance becomes clearer. This is shown in Table I. High motor performance (flight, running, diving) is thus correlated with high relative blood volume. So much, but no more, can be concluded from this comparison.

Blood volume in man

A. Reference standard. First we must ask a simple question, to which the answer is not so simple, however: What is the standard of reference against which capacity must be measured? In comparison with healthy animals, man is subject to considerable variations in body weight in proportion to height as a result of the pathologic deposition of fat or retention of water, of cachexia, or of total immobilization. This problem must be considered and solutions proposed, since it is obviously not enough to regard a value merely longitudinally; it must also be related to the ideal value. If body weight and height are in reasonable proportion, *the blood volume will be 7.7 per cent of the body weight in kilograms.* In this case we can also apply the formula whereby the body weight in kilograms is equal to the number of

From the Department of Medicine, Kantonsspital Liestal, Switzerland.
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Table 1

Genus	*Motor behavior build*	*Blood volume in per cent of weight*
Planorbis (mollusca)	Limited movement open circulation	58
Cottus (teleost)	Air bladder	1.5–3.0
Squalus (selachian)	Strong movements necessary for stabilization	5.[illegible]
Lacerta (reptile)	Vigorous movements for short periods horizontal axis	3.0
Small birds	Relatively heavy heart	8.0
Wild duck	High arterial pressure high temperature and rapid pulse	13.2
Wild rabbit	Burrows does not run	4.4–5.5
Hare	Runs	7.5
Dog (in general)		7.[illegible]–9.5
Greyhound		Up to 13.6
Horse halfblood		5.6–6.6
Thoroughbred		10.2–13.6
Bat	Flight season	13.0
	Hibernating	5.0
Seal	Diving	11.0
Sperm whale	Diving	10.0
Macacus rhesus		5.8
Hominide	Upright gait	8.2
Homo sapiens	Newborn	7.7
	Adult male	7.5
	Adult female	6.5

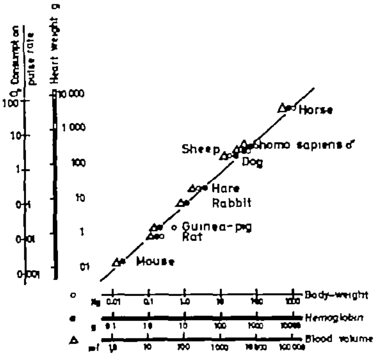


Fig. 1 Correlations of blood volume hemoglobin and body weight to heart weight and oxygen consumption/pulse rate. Diagram modified from Sjostrand Forum Cardiologicum 3 November 1961 Mannheim Boehringer by permission

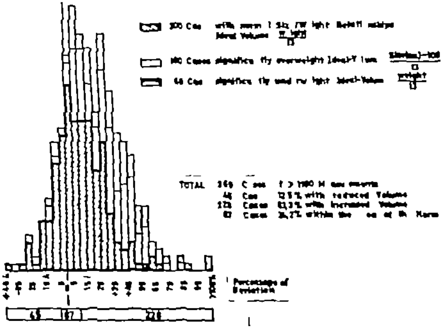


Fig 2 Distribution of blood volume measurements in relationship to the norm Columns show equal deviation

centimeters by which the height exceeds 100 Thus

$$\frac{\text{Body weight in kg}}{13} = \frac{\text{Height in cm} - 100}{13} = \text{Blood volume in kg}$$

Out of 1 100 subjects we found only 200 with a good height/weight ratio This is hardly surprising in hospital patients Their distribution according to deviation from the norm is shown in Fig 2 It will be seen that more are above the norm (greater blood volume) than below (reduced blood volume) Where

$$\frac{\text{Body weight (kg)}}{\text{Height} - 100 \text{ (cm)}} > 1\,0$$

difficulties arise If the standard blood volumes are calculated from

$$\frac{\text{Weight (kg)}}{13}$$

the levels will be too low If the volumes are reckoned according to height however the results will correspond to the distribution obtained with a good height/weight ratio The opposite occurs if underweight subjects are classified by standards obtained on a height basis (Fig 2) Therefore two postulates must be made for calculating standard blood volumes (1) For subjects with a good height weight ratio and for underweight subjects the standard value must be calculated from

$$\frac{\text{Weight (kg)}}{13}$$

(2) For overweight subjects the standard must be calculated from

$$\frac{\text{Height (cm)} - 100}{13}$$

The diagram in Fig 2 proves that we need the two different reference methods for determination of the ideal volume and we find thus a corresponding distribution in the three groups

B Normal range A height/weight ratio is regarded as normal when it does not exceed the norm by more than ± 5 per cent i e

$$\frac{19}{20} < \frac{\text{Height (cm)} - 100}{\text{Weight (kg)}} < \frac{20}{19}$$

It is obvious that supranormal values are not only much more frequent but also much more important clinically than subnormal ones The limits of the pathologic must therefore be set correspondingly

Losses of blood are not tolerable to the same extent as true excess filling of the vascular space and the limits of normal have to be fixed according to these extremes. Having found the appropriate standard therefore we consider without statistical confirmation the following deviations to be of pathologic and clinical significance. Pathologic increase in blood volume from +12 per cent, pathologic decrease in blood volume from −6 per cent.

C. Deviations found in man. We cannot go into detail here but let suffice an indication of the conditions which may give rise to an increase or decrease in normal or sick persons. *Decrease*—age, lack of training, inactivity, cachexia, extravasation, endocrinopathy (hypothyroidism). *Increase*—growth, training, pregnancy, adaptation to hot climate, adaptation to hypoxic atmosphere, hyperthyroidism, hemodynamic disorders (septal defect, decompensated cor pulmonale, some forms of cardiac insufficiency). A universal explanation is not yet possible. We can only refer to conditions of reduced capacity or adaptation to increased motor performance.

Blood volume and circulatory events

These findings justify our saying that increased over all motor performance over a long period requires a larger volume of blood. It must also be said however that certain pathologic states, especially those involving a hemodynamic disturbance, may lead equally to an increase in blood volume. Admittedly these are conditions in which a pathologic state of equilibrium has been reached.

Changes in blood volume are thus seen in both healthy and sick subjects but always stabilized over a long period. *We shall discuss only these long term adjustments.* Achievement and maintenance of the new balance is the same whether it was dictated by the need of a healthy body under extraordinary external circumstances or whether it was the need of a sick body for compensation. The exact significance of the volume of blood for the circulation or rather for vascularization cannot yet be determined. For this physiologic considerations and a fresh approach to the problem are necessary. It is clear however that we must find a universal explanation for high volumes of blood in certain species, increased volume in adaptation of the healthy organism and the long term stable hypervolemia in pathologic states. We are regarding blood in this context merely in terms of volume as material filling a closed vascular system and are ignoring its other properties, e.g. solvent volume or suspension of cells.

Blood as mediator between the cell and the outside world is brought to the parenchymal cells by the circulatory apparatus as and when the short term and long term needs dictate. The pressure under which the blood irrigates the consumer cells is very low and the flow in the parenchyma is determined by specific mechanisms (microcirculation). The vascular system presents three components: (a) region comprising mechanisms for differential supply (high pressure region), (b) region for utilization and metabolic activity (capillary region) and (c) region for vascular return (low pressure system).

Relationships of pressure and flow are as varied in the different sectors as are the functional and regulatory principles. This variation becomes evident as soon as we consider the distribution of the blood in the system. Where is the mass of the blood to be found? Fifteen per cent of the volume is in the systolic left ventricle, in the large and small arteries (high pressure region). Five per cent of the volume is in the capillary region. Eighty per cent of the volume is in the low pressure region (55 per cent in large and small veins, 25 per cent in the right ventricle, lungs, left atrium and diastolic left ventricle).

These facts enable us to state: *The capillary region* contains little blood and receives only one stroke volume for each complete circuit; it is independent of the total volume. *The arterial segment*, which is under high, rhythmically renewed pressure, contains a small portion of the blood; its volume is not dependent on the total blood volume but on the stroke volume and the elasticity of the vessels. Intracirculatory parameters are the stroke volume and the mean aortic pressure. The long term parameter is the minute volume established by a stroke volume which may be smaller or larger. Thus events in the

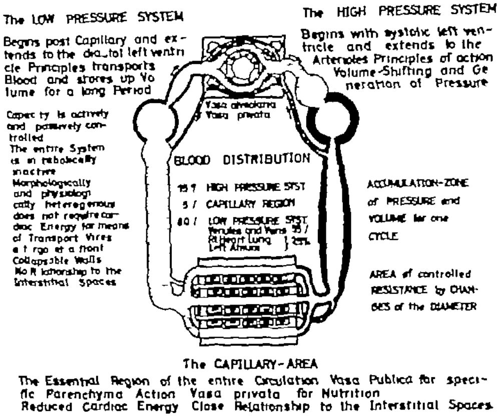


Fig. 3 Properties of the circulatory areas

arterial segment appear to be quite independent of the blood volume and in fact they are so long as the volume of blood required is available to the left heart. Therefore it is in the mechanism and performance of the low pressure system that we must look for the functional properties involved and the principle of their maintenance. For this purpose we must again consider the special features of the regions that we have defined (Fig. 3).

A. High pressure region. This region represents a reservoir of pressure and volume. During systole pressure is raised from the diastolic to the systolic level and a given stroke volume is forced into an elastic system. During diastole the additional pressure (the pressure amplitude) and the additional volume (the stroke volume) are discharged. There is no transmural pressure and the increase in pressure exists only in the segment in which volume and pressure are stored, the so called Windkessel or pressure chamber. It is considerably reduced on entry into the parenchyma by increased resistance, i.e. constriction of the arteriolar lumen. This reserve of pressure and volume serves the diastolic interval and also provides the means of preferential supply to any vascular region at short notice. The existence of this reserve is essential to the control of blood flow by vasodilatation. Only in this way can preference be given to a parenchyma and the flow be directed. The need for such rapid adjustments of supply to a certain region arises for instance in the case of flight. The only intracirculatory factors involved in this control are the stroke volume and the pressure, not the total blood volume. *The unit of time within the arterial system is the interval until the next contraction.*

B. Capillary region. In the capillary region the pressure is very low and is often influenced by transmural factors. Here the microcirculatory characteristics of each particular parenchyma are decisive, especially for the vasa publica, the responsible for organ functio

capillary region receives a single stroke volume with each contraction of the heart, thus a relationship to the total blood volume is impossible. Nor does the stored pressure affect the capillary region as a whole, only selected areas of it, and then only in an emergency.

C. Low pressure region. This region is the vascular return system. Analysis of structure and function has proved difficult, has only recently been undertaken, and seems to be still incomplete. It is astonishing that the simple return of the blood to the heart involves such varied structures and forces. The following details may be mentioned: (1) In the whole region, with the exception of the right ventricle and the pulmonary arteries, pressure is low. The gradient is small. (2) *The walls are flexible*; transmural pressure often exceeds internal pressure over considerable stretches and causes the vessels to collapse, *interrupting the flow*. (3) The profile and not only the surface area affects blood flow. (4) Even the smallest variation in resistance affects flow. (5) Only minimal traces of cardiogenic pressure affect the return flow. Vires à fronte et a tergo are effective. (6) The upright posture makes considerable demands on the energy for venous return from great parts of the body. (7) There is a discontinuous flow in the periphery due to local muscular forces and the existence of venous valves. (8) In the thorax, changes in pressure are induced by respiratory movements of the diaphragm and the volume of blood rapidly leaving the thorax. Because the central veins are pliable, they function as reservoirs since their contents can change rapidly through a partial collapse of their walls. They form a collapse chamber[1] and thus contribute to the transformation of the steady flow from the tissues into the pulsatile flow at the atrial entrance which is needed for the discontinuous cardiac filling. (9) The right ventricle raises the pressure, reduced to a minimum in the right atrium, to a level which enables the blood to pass through the lungs.

The great structural variety and the involvement of numerous extracardiac forces (muscles, gravity, diaphragmatic movements, voluntary actions such as coughing) will be recognized. The chief characteristic is the *distensibility of the system* which allows a storage capacity two hundred times greater than that of the arterial segment. This means that the same additional pressure which stores, for example, on the arterial side one unit of volume would store in the low pressure system 200 units. Such a system can never be subject to the same functional laws as the arterial system.

Mean circulatory filling pressure

The difficulty of understanding the processes in the low pressure region and of estimating the strength of the forces involved has led to the resurrection of quite simple, forgotten concepts. Starling talked about "filling pressure" as long ago as 1897; this idea was taken up again by Starr in 1940 and later given a new meaning by Guyton in 1954. If the circulation is arrested, the pressure in different parts of the vessels levels out. Blood is transmitted from the high pressure region in the arterial segment to the capillary region and from there to the venous segment. The final pressure is *less* than arterial pressure and *greater* than intravital pressure in the right atrium, the site of the lowest intravital pressure. Thus during life differences in pressure, both upward and downward, are produced and maintained. It is clear that after death this pressure becomes accessible.

How is this pressure produced? It is produced by *the intravasal blood volume* and by *the tonus produced by the muscular activity of the vessels*. Tonus and volume are thus the factors which determine the mean circulatory filling pressure (MFP).

How can volume act as pressure? Under the condition that the container is elastic, the addition of volume is possible. This addition will increase the pressure in the container in proportion to the additional volume and the elastic properties of the wall of the container. The increase in volume by augmentation of the tension of the wall increases pressure. These determining factors are held constant for different periods, the tonus for short lengths of time, blood volume for longer. By transforming blood into a *component of pressure* we make it easier to understand it as a circulatory parameter.

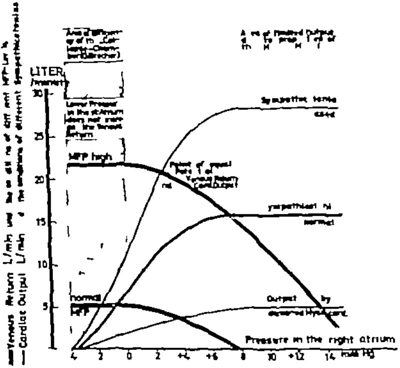


Fig. 4. Venous return and cardiac output as a function of the pressure in the right atrium. Modified diagram based on the figures of Guyton and colleagues and Krug and Schlicher (by permission).

The pressure which becomes evident after death is obviously also present and effective during life. It is merely masked by superimposed intravital influences. That it exists is proved by its very definition, since venous tone and blood volume certainly exist. Increasing the blood volume increases the MFP. But what effect does altering the MFP have intra vitam? This determines the possibility of venous return to the right atrium, the *return potential*. If by any kind of vital activity pressure can be lowered in the right atrium, the gradient will be *increased if MFP is high* and other parameters are constant. If in illness for any reason pressure in the right atrium cannot be kept at a normal level, venous return must decrease *if* MFP remains normal and finally cease altogether when a pressure equilibrium is reached and no gradient at all remains. This situation, however, is fulfilled respectively in an individual trained for high performance and therefore requiring a large volume of blood, and in certain cardiac patients whose circulation is in pathologic equilibrium and whose MFP is raised by an increased volume of blood in order to maintain a gradient toward the right atrium despite the increased pressure there. The improved gradient to the right atrium increases the supply of blood to the left heart and thus the potential output.

MFP is normally about 7 cm H_2O but can go much higher, as we shall see. Guyton and associates have shown diagrammatically the relationship involved (see Fig. 4). Although these are not measurements obtained in man, they nevertheless present in an extremely clear manner the processes which must be involved in these complex shifts in pressure and volume. We see that both potential of venous return and potential of output depend on the pressure in the right atrium. The value of the real shifting of volume is given by a point at which both lines of actual potentials (venous return and cardiac output) *cross*.

With constant average intra-atrial pressure, wide variations in return and output potential arise, depending on the MFP

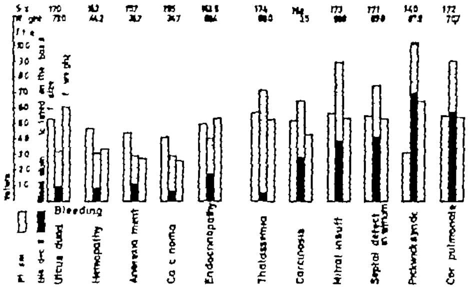


Fig 5 Pathologic blood volumes

Each MFP and each atrial pressure value has its corresponding return potential. The effect of the MFP is limited by the thoracic blood reservoirs (collapse chambers) already referred to in so far as this interruption of the circulation under the influence of strong negative intrathoracic pressure prevents the MFP however high from exerting its effect. On the other hand the material characteristics of the heart set a limit on cardiac output whatever the effects of inotropic sympathetic tonus. It is clear however that even without the loss of blood venous return and cardiac output can decrease if venous tone decreases. We cannot here discuss the more intimate atrioventricular dynamics nor the laws set by the properties of the contractile tissue. Recently K Wezler established the diastolic tonus of the heart as a new mechanical element. None of these superimposed features modifies the gradient formation carried out by MFP intra vitam. Blood volume is thus recognized as one of the factors that determines MFP a pressure which during life is masked by many factors but which ultimately determines the gradient to the point of lowest average pressure in the right atrium. This gradient is also determined however by the ability of the organism to maintain low pressure in the right atrium. This ability involves all the properties and regulatory functions of the contracting substance. Blood volume therefore is a dimension which manifests itself as a pressure remaining constant over long periods. Within certain limits this pressure determines the potential of the turnover.

Clinical observations and results

It has been established that an increased volume of blood raises MFP and that the resultant increased gradient to the right atrium permits a higher rate of circulatory output. This is not to say that other factors may not require a primary increase in the size of the intravascular fluid space. A larger solvent space might for instance be required on metabolic grounds. Clinical findings cannot all be explained on a hemodynamic basis as has been shown in earlier publications. Fig 5 shows examples of cases of pathologic volumes. We see that there are many possibilities of deviation.

Cases in which the blood volume is increased include the following pathologic conditions (a) hemodynamic anomalies in the low pressure region—decompensated cor pulmonale mitral decompensation septal defect with left right shunt complete cardiac insufficiency (b) anemia usually in terminal stages (c) cachexia manifesting hydremia (d) polycythemia. *Reduced blood volume is found in* (a) extravasation (b) endocrine disorders e g hypothyroidism (c) pathologic immobilization.

Difficulties in regard to the standard

value must always be eliminated by applying the rule that the ideal volume should be calculated from the height for overweight subjects and from the weight for underweight subjects. Figs. 2 and 5 show these results.

Longitudinal studies, i.e. values determined at different times and under different conditions in the same person, are of greatest interest. From such studies certain highly probable conclusions emerge.

Venous and intra-atrial pressure during life and after death

We have attempted to obtain evidence for a correlation between blood volume and MFP from measurements practicable under clinical conditions. Even so these measurements required very special circumstances and so could not be carried out everywhere and at all times. We determined conventional venous pressure, hydrostatic pressure in the central veins or in the right atrium by means of catheterization, and in a few cases pressure in the right atrium by means of atrial puncture, the site of which was verified in all cases at autopsy. For all measurements the point of reference was taken as the middle of the atrium 4 cm below the level of the sternum. From this point the hydrostatic columns were measured. Before death hypocoagulability was obtained with heparin.

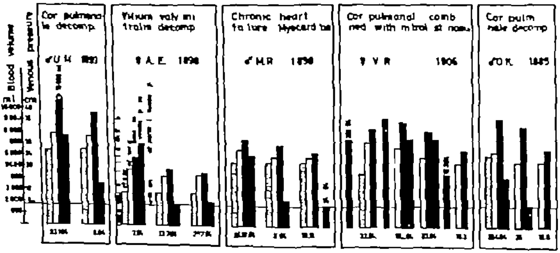


Fig. 6. Blood volume and venous pressure during cardiac and diuretic treatment.

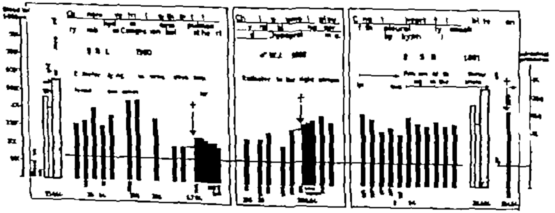


Fig. 7. The manifestation of the mean circulatory filling pressure (MFP). Catheter measurements were made in the vena cava or in the right atrium. The relationship to intra-atrial pressures were measured intra vitam

It seems to be possible in this way to measure MFP after death. This pressure appears quite rapidly and is higher than intravital pressures. Its relationship to the intra-atrial pressure during life is evident.

The diagrams should prove the following: (A) Relationship between venous pressure and blood volume (Fig. 6). Longitudinally, the rapid reduction in venous pressure and the slower reduction in blood volume are evident. Venous pressure is here a rough indicator of MFP. The problems associated with reference standard are seen from this and subsequent figures. (B) Manifestations of MFP (Fig. 7). Here the central veins or the right atrium were catheterized usually for therapeutic purposes. Mean intra-atrial pressure was measured long before death under a variety of hemodynamic

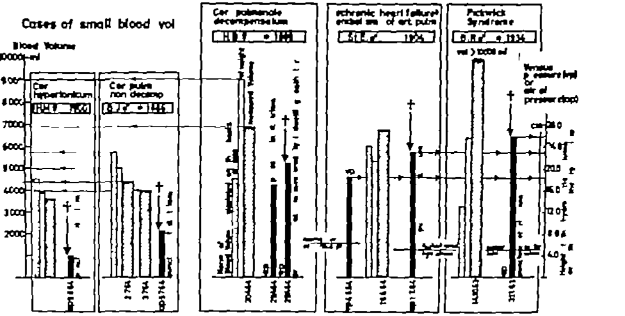


Fig. 6. Venous pressure intra vitam and intra-atrial pressure postmortem (MFP) in relationship to blood volume.

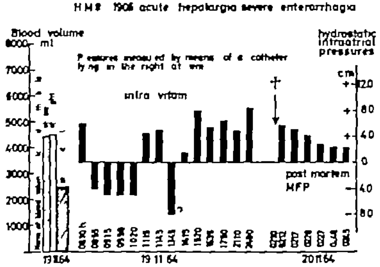


Fig. 7. Intra-atrial pressures intra vitam and postmortem by [illegible] state of reduced blood volume.

conditions After death an increase in pressure was observed followed by a slow decrease as venous tone fell (C) Venous and intra atrial pressure with normal and increased blood volume The correlation between MFP and blood volume is demonstrated See the extreme values in the Pickwick syndrome (Fig 8) (D) Intra atrial pressure with extremely small blood volume (Fig 9) It is obvious how pressure in the atrium during life is modified by respiration heart action and the wide variations in venous congestion After death a very low MFP is noted in this case and it falls further to 2 5 cm one tenth of the pressure observed in Case 5 of Fig 9

These observations confirm therefore in so far as this can be done experimentally under clinical conditions the theory that blood volume represents a pressure regulating factor

We cannot enter into the great problem of general heart failure but we see that this state is not due alone to insufficiency of production of pressure or to a shifting of volume by the left ventricle A disturbance of each of the other factors which normally contribute to a perfect performance of vascularization can cause a kind of failure That is also true for venous return and for MFP

Summary

1 Blood volume is correlated in each genus and each individual with the general motor behavior High motor performance in a genus or adaptation in man requires a large relative volume of blood

2 The significance or effect of the vascular volume must be sought in the structures and function of the low pressure region This region subjected to the principle of volume regulation represents a sequence of widely varying structures receiving widely varying *noncardiogenic influences* upon venous return Flow is subject to various discontinuities

3 Mean circulatory filling pressure (MFP) is found to be an important dimension in the low pressure region It determines the maximum gradient and therefore the potential supply to the left heart Return potential becomes a function of intra atrial pressure and MFP

4 MFP is determined by blood volume and venous tone both of which are accessible to therapeutics Blood volume appears to decrease only when a permanent increase in MFP is no longer necessary

5 Calculation of the ideal blood volume presents difficulties The height should be used for overweight subjects and the weight for underweight subjects Limits of clinical significance are −6 per cent and +12 per cent

6 A few examples of determinations of MFP in man are presented The relationship to blood volume is evident

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Antiarrhythmic drugs

Part I Mechanism of quinidine action

Alan F Lyon M D[*]
Arthur C DeGraff M D[**]
New York N Y

Quinidine is properly considered to be the prototype of antiarrhythmic drugs As in the case of many other medically active alkaloids the clinical demonstration of its effectiveness long predated any knowledge of its mode of action or even of its structure

Quinidine like quinine is contained in cinchona bark and was used by Peruvian Indians for the treatment of malaria Quinidine was introduced in the nineteenth century as an antipyretic and early in this century as an antiarrhythmic drug It also has mild local anesthetic properties which are of no clinical importance It is the D isomer of quinine which is a complex organic molecule composed of a quinoline ring joined to a quinuclidine ring by an alcohol linkage Both rings are polycyclic and contain a nitrogen atom in the ring The nitrogen atom in the quinuclidine is in the tertiary form and has a positive charge at physiologic pH

Although the mode of action of this molecule is still not precisely understood a great deal of useful information about its action is now available

Quinidine has the property of actively binding to a variety of proteins (probably through the quinoline ring) but it is not likely that this can supply a unitary and complete explanation for all its actions Thus manipulation of the pH can dissociate the antiarrhythmic contractile and peripheral vascular effects Moreover chemical blockage of the tertiary nitrogen on the quinuclidine ring can block the antiarrhythmic effect and similar quinolines without the tertiary nitrogen show similar contractile and blood pressure effects and are devoid of antiarrhythmic activity

At a metabolic level quinidine interferes with the utilization of glucose and fructose possibly at phosphorylation It reduces the activity of a wide variety of enzymes including various ATPases hydrolytic glycolytic and oxidative enzymes The relationship of these metabolic effects to its clinical action or toxicity is unknown

Quinidine exerts a profound effect on cell membranes where it disturbs the passive flux of potassium and sodium and probably of calcium These effects are well established and of critical importance to the antiarrhythmic action of the drug but the precise cause of the interference with ion movement is not known It may be that by its metabolic effect on enzymes such as ATPase it limits an energy requiring ion accelerating mechanism An alternate possibility is that in binding to the membrane the positive charge of its tertiary nitrogen may be so located as to interfere with cation transfer The suggestion has also been made that because

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*Cardiac Therapy Research Center Veterans Administration Hospital 130 West Kingsbridge Road Bronx N Y 10468
**Department of Therapeutics New York University School of Medicine 550 First Ave New York N Y 1

produced by quinidine could logically terminate such arrhythmias. A prolongation of refractoriness would allow the impulse to reach tissue that is fully refractory and stop the circus movement. It is widely held that this is the major effect of quinidine; in this view the depolarization block and decrease in conduction velocity produced by quinidine are considered to be unfortunate because they allow more time for normal repolarization to occur. Cogent arguments can also be presented for the importance of slowing conduction velocity to the point of extinction.

Electrocardiographic evidence favors the repolarization effect in that the QRS group widening is not usually present when an arrhythmia is controlled, although some Q-T or Q-U abnormality is usually present. On the other hand, in the laboratory, depolarization block is usually quite prominent at the time of control, whereas prolongation of the action potential (intracellular evidence of repolarization delay) beyond that appropriate to rate is inconstant. In favor of the importance of the repolarization effect is the fact that in experimental situations a very low concentration of extracellular potassium or the addition of acetylcholine, both of which increase the loss of intracellular potassium, will block the effect of quinidine. However, it is likely that there is competition between Na^+ and K^+ for entry during depolarization, so that a lowering of plasma K would help Na^+ entry.

The complexity of the problem is demonstrated by an animal study which showed that transitory fibrillation, such as may be produced by acetylcholine or hypothermia, can be controlled by atropine or Banthine, drugs that produce repolarization block but not depolarization block. Persistent fibrillation of recent origin could be controlled by procaine amide, quinacrine and certain antihistamines, drugs that produce prominent repolarization block and only moderate depolarization block. Chronic fibrillation, on the other hand, requires quinidine, which prominently produces both depolarization and repolarization block.

It is clear that despite a great deal of fundamental research, the present state of knowledge of the mechanism of quinidine makes its use, to a considerable extent, empirical.

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Annotations

Hypotension from beta adrenergic blocking drugs

Ahlquist in 1948 proposed the division of the sites of adrenergic action into alpha and beta receptor groups although the concept of inhibitory and excitatory receptors for adrenaline can be traced back to Dale who noted that ergot blocked only the excitatory actions while not affecting the inhibitory actions of adrenaline. The results of stimulating the beta receptors include adrenergic effects on the heart, relaxation of bronchial muscle and vasodilatation in certain vascular beds whereas the results in the alpha group include contraction of smooth muscle such as vasoconstriction. Norepinephrine was found to exert almost pure alpha effects, isoproterenol almost a purely beta action and epinephrine both. The classic adrenergic blocking drugs such as ergot, phenoxybenzamine and phentolamine block only the alpha receptors; they do not prevent the inotropic and chronotropic effects on the heart. The first agent discovered which blocked the beta receptor was dichloroisoproterenol. However, it was soon shown to have potent sympathomimetic effects of its own.

The animal pharmacology of pronethalol (nethalide) was described by Black and Stephenson in 1962. It is a beta receptor blocking agent which is free from sympathomimetic activity. They found that after slow intravenous administration in anesthetized cats it produced a slight fall in blood pressure that was associated with peripheral vasodilatation whereas rapid injection was followed by myocardial depression with a sharp fall in blood pressure. The action in man is consistent with beta receptor blockade. The dilatation of the blood vessels of the forearm after intra-arterial isoproterenol is abolished and the response to intravenous epinephrine is altered so that it resembles that to norepinephrine. Pronethalol reduces the tachycardia during the effort phase of the Valsalva maneuver and diminishes the overshoot of blood pressure that follows release. This drug has been tried in a variety of clinical conditions: arrhythmias,[10,11,12] angina,[3,20] pheochromocytoma, obstruction of the outflow tract of the heart,[11] and hypotension after prolonged metaraminol.

Dornhorst and Robinson[10] found no constant effect on the blood pressure after intravenous infusion of pronethalol. This has been confirmed although an increase in forearm blood flow was found for the duration of the infusion.[16] Prichard described a hypotensive action of pronethalol after prolonged oral administration. He cites unpublished data from a double blind trial of pronethalol in patients with angina pectoris in whom the supine blood pressures averaged 8.3/5.7 mm. Hg lower on pronethalol than on placebo ($p < 0.05$). The mean standing diastolic pressure was reduced by 4.8 mm. Hg ($p < 0.05$) and the mean standing systolic pressure by 6.5 mm. Hg ($p > 0.05$). Each patient received both placebo and pronethalol for two fortnightly periods in randomized order. Thus the maximum continuous time of administration of pronethalol was 4 weeks. Schroder and Werkö[?] made various hemodynamic measurements before and after 1 week of oral pronethalol. In 10 hypertensive patients supine blood pressure fell from a mean of 189.3/102.8 mm. Hg to 171.1/95.5 mm. Hg but were unaffected in 8 normal subjects. Prichard treated 15 patients for 3 months; 11 were hypertensives and 4 were normotensives who were receiving the drug for angina pectoris. The mean fall in blood pressure for the 15 patients after pronethalol was 33/23 mm. Hg supine and 27/16 mm. Hg standing. Three of the hypertensive patients received no other drugs whereas the remainder were on other hypotensive agents (guanethidine, bethanidine, reserpine or chlorothiazide alone) unaltered for the duration of pronethalol administration. In each of the patients there was a fall in blood pressure with the absence of postural hypotension. This hypotensive action of pronethalol was not further investigated in view of its tumor producing action in mice.

Recently the pharmacology of a closely related drug, propranolol (I.C.I. 45520), was described by Black and associates. It has a beta receptor blocking action in both animals and man about ten times as potent as pronethalol; it does not produce tumors in mice or in any other experimental animal. Initial studies by Prichard and Gillam have shown that propranolol has a hypotensive effect after prolonged oral use although, like pronethalol, it has no such action after intravenous injection.[30] It was given to 23 patients for periods of 2 to 7 months. Seven patients were normotensives who were receiving the drug for angina pectoris; 5 of these showed a fall in blood pressure. Four of the 16 hypertensive subjects (7 of whom also had angina) were hitherto untreated, 3 patients were transferred from other drugs and the remainder of the patients were continued on their previous hypotensive drugs (guanethidine, bethanidine, methyldopa, reserpine or chlorothiazide alone). In all except one anginal patient already well controlled on chlorothiazide alone there was a fall in blood pressure after the administration of propranolol. The mean blood pressure for the 16 hypertensive patients before propranolol was 183/104 mm. Hg supine and 171/108 mm. Hg standing. After the drug it was 162/89 mm. Hg supine and 137/89 mm. Hg standing. In patients receiving no other drug the ...

a fall in the supine and standing pulse rates. No exercise hypotension was seen in 7 nonanginal hypertensive patients who had supine and standing diastolic blood pressures of 100 mm. Hg or less.

Side effects with the administration of propranolol were not troublesome. In the dose recommended for the treatment of hypertension, up to 200 mg. a day in divided doses three or four times daily, the only side effect has been slight tiredness in 2 patients. However, 1 anginal patient developed heart failure 2 days after starting propranolol. She recovered without further treatment after stopping the drug. Heart failure has been reported to follow the use of pronethalol.[18]

Beta receptor blocking drugs have no hypotensive effect when given intravenously;[8,10] they have only a small effect after short term oral administration,[19,20] but a considerable effect after prolonged oral use of from 2 to 7 months.[14] Both pronethalol[14] and propranolol[9] acutely modify cardiovascular reflexes, as shown by their reduction of the tachycardia during the effort phase of and the overshoot of blood pressure after the Valsalva maneuver. A feature of both drugs has been the absence of postural hypotension in those patients receiving the drugs for 2 months or more. This would be expected since the response of the cardiovascular system to gravity is mediated by an increase in sympathetic (alpha) vasoconstrictor tone. In addition, there is no exercise hypotension after the administration of propranolol. Although no studies on cardiac output have been performed after prolonged administration of beta receptor blocking drugs, after 1 week of pronethalol[20] there was reduction in the cardiac output at rest in hypertensive patients but not during the response to exercise. After the acute administration of pronethalol to normal subjects no definite effect on cardiac output was seen.

Beta receptor blocking drugs may act centrally, but it has been suggested that their action may be due to blockade of the sympathetic nerves to the heart. The suggestion has been made that these drugs act by reducing the cardiac response to various stimuli that are responsible for transient rises in blood pressure. This is seen in the modification of the Valsalva maneuver. To explain the absence of any acute hypotensive action it is thought that the baroreceptors may be gradually conditioned by the damping down of pressor responses to regulate the blood pressure at a lower level. The cardiovascular responses that are dependent largely on alterations in vascular tone are unimpaired. This is manifest in the relatively normal response to exercise and posture in patients receiving these drugs.

In conclusion, although the hypotensive action of pronethalol could not be exploited because of its tumor producing effects in mice, propranolol is free from this disadvantage and, in addition, appears to have a wider therapeutic ratio.

B. N. C. Prichard, M.Sc., M.B., B.S.
Med. of L...
University College Hospital Medical School
University St. ...
London, W.C.1, England

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The necessity for effective dental health service in cardiology

In almost all ailments of the heart caused by bacteria the source of the infection is known to be the pathologic and infected environment of the teeth. Bacteria are driven into the blood stream (bacteremia)[1-4] from such foci by extraction, other operative procedures, and by hard chewing. Subacute bacterial endocarditis is perhaps the best example. Kerr's monograph listing 800 references provides an excellent key to the literature relative to this disease. From 80 to 90 per cent of the cases occur in persons whose heart valves and endocardium have been damaged by rheumatic heart disease. Congenital heart disease and congenital anomalies account for a few cases.

The two principal diseases involving the teeth and their surrounding tissues—caries and periodontoclasia—are for all practical purposes entirely preventable. Prevention of these dental diseases should also prevent those diseases of the heart in which the infection comes from such foci. Under these circumstances the health, welfare, and even life itself of persons who have heart conditions which predispose to infection may depend upon prevention and control of dental disease. It is the responsibility of the cardiologist to know that this is possible and necessary and to make sure that the risk to his patients is thus reduced or eliminated.

Caries is a source of bacteremia only and then temporarily from advanced-stage lesions involving infection of the pulp. Bacteria in the periodontal pocket and in the diseased periodontal tissues are the source of almost all bacteremia from the environment of the teeth.

Periodontoclasia is a universal disease of man originating as gingivitis in childhood, continuously advancing during adulthood, and never ending so long as any teeth remain. With the exception of those few persons who have learned and continuously follow the only entirely effective method of personal oral hygiene ever known, every dentulous adult now has demonstrable active advancing periodontoclasia (pyorrhea) lesions in some stage about most or all of his or her teeth. This includes all heart patients and incidentally also all dentulous cardiologists.

Both caries and periodontoclasia are caused by microscopic organisms, the lesions at first are microscopic in extent, they advance microscopically, the tissue involved are composed of microscopic elements, and the destructive processes are microchemical. Employing techniques and methods acquired through many years of medical laboratory teaching and research concerned with microorganisms and microscopic pathologic conditions, I secured and have published (listed in Reference 13) accurate essential information as to the *important* microscopic etiological and pathologic conditions at the particular locations where the lesions of caries and where those of periodontoclasia[11] originate and advance. Some vital parts of this information had not been clearly recognized or definitely understood theretofore.

On the basis of this factual information and after much microscopically controlled experimentation, I designed and have taught and published[12,13] the method of personal oral hygiene which according to all that is now known is absolutely necessary and which for all practical purposes is entirely effective for the prevention and control of these two diseases. *The teeth must be effectively cleaned* daily with the right kind of both toothbrush and dental floss at the specific locations where the lesions of these diseases originate and advance.

This necessary method of personal oral hygiene is different from, and in some vital particulars is quite the opposite of, other methods generally taught and followed, all of which are inadequate and unsuccessful. Witness the great prevalence of these diseases. It has not been taught in the dental schools.[14] Indeed, some of the facts as to the exact local microscopic etiological conditions involved which have to be prevented have not been recognized or taught. Therefore those dentists who are now prepared to provide and promote the only entirely effective method of prevention presently known have had to obtain some of the necessary information since they graduated.

Each person must be instructed individually and must be shown the diseased or vulnerable locations on and around his or her teeth and exactly how to clean them at these particular locations. This can be done *only* by a dentist who knows how and understands why it is necessary and who is willing and prepared *to teach his patients as an important part*

of his dental health service. He would be following the exact method in the home care of his own teeth.

The relationship of dentistry to cardiology has been recognized.[19,20] The cardiologist must have the cooperation of an informed dentist who has the necessary information for effective prevention and elimination of dental disease as a source of infection in especially predisposed patients.

The importance of dental health is emphasized in the Department of Medicine at the Tulane University Medical School. The instructor in oral hygiene, a dentist, shows each sophomore student the diseased and vulnerable locations in his own mouth and teaches him exactly how and why to clean them at these locations. Those who follow our method will be able to maintain the highest degree of oral cleanliness and dental health. Those who become cardiologists later will then know what their patients need in this regard.

Anyone who wishes to do so can confirm the factual information upon which the prevention of dental disease must be based. Clinical confirmation is easy. Persons can be found here and elsewhere who by following our method of personal oral hygiene have maintained the highest degree of dental health for years. I can point to a 90-year-old man who for more than 15 years has maintained practically 100 per cent oral cleanliness and dental health. The average medical student produces more pus (pyorrhea) around some of his teeth in a day[22] than this old man produces around all of his teeth in a month.

Comment. I believe that at some time in the future leading cardiologists will wonder, in retrospect, how information so greatly needed by many of their patients could have been overlooked or neglected for so long.

Summary. The environment of the teeth is the principal source of infection in bacterial diseases of the heart. Periodontoclasia is a universal disease of all dentulous people. Therefore persons who have damaged heart valves or are otherwise predisposed to bacterial heart disease now have demonstrable active periodontoclasia about some or all of their teeth. This source of infection can be eliminated by dental health care which includes an effective method of personal oral hygiene, but not without it.

Charles C. Bass, M.D.
Dean Emeritus and Professor of Experimental Medicine, Emeritus
Tulane University School of Medicine
New Orleans, La.

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A simple method for the recording of radiopaque dilution curves during angiocardiography

The alue of angiocardiography and of dye-d lution methods as independent techniques n the diag nosis of heart diseases has lready been well es tablished

The combination of both method that is the use of the radiopaque material indicator and the continuous recordin of the hanges in x ray den ity of the different heart hambers and essel during the pa sage f the tr st medium offers some important ad antages These advantages are in general the pos bilt f a more refined quanti tative e aluat f ncargiocardi grams or direct mon a r f ams nd especially the pos bility of re d m lcator-dilution urves from any hea h ber r essel as desired w thout the need f t n of all these different sites n order t t samples of blood

An h t wh h fa ors the combined tech ique h f t that no a lditional equipment t q p rison with the separ te uses of he th d

[illegible] procedure to record radiopaque [illegible] or e ltr n or after angi ard graphy [illegible] The n c urin es (for Cardiogreen or blue [illegible] the d e-dilution device s used to onne t with the CC-oximeter and the Micro-graph bght sen it a direct writing recording ystem The onl modification which has to be made the d sconnection of the light sources within the me ar ng ey (which is easily done) in order to cut ff the lifferential photocell normally used for compensation (On the other hand a separate differential photocell can be connected in order to compensate for non pecific den ty changes) After this modificat n one or more photocells can be placed on ( ) the x ra screen (b) on the screen of a television m nitor used in connection with image intensification or (c) w thin the cone of light of a projected cineangi cardiographic moving picture film The phot sensitive receptors ha e to be ad justed to the projection of that heart ca ty or essel of which the hanges in density should be analyzed The use of other s parate photoelectric transmitters DC amplifiers n l ph toelectric re cording tems is also pos ble and has certain advantages in recordin multiple dilut n curves with other reference tracings (ECG pres ure)[1]

In men the direct fluoroscopic m thod i indicated because an angiocardiogram cann recorded imultaneou ly Cineangio-project [illegible] tele ion method are equally useful the la t method especiall f tape recordin and reproduc t on of the angiocardiogram pos ible Repet tiv e aluation of projected ineangi grams i at the moment the most pra tical wa f recording radio paque dilution curves

The shape of the recorded radiopaque d lution urve depends part from the hemodynamic situation on the site the volume and oncentration of the injected opaque material and the localiza tion of the photosensitive pickup Superposition of the different heart chambers and essels h e to be oided in order to get pure curves which are of typical shape height timing and duration in the different part of the circulation Such tracings will be publi hed elsewhere[2] They allow l al circulation times between the heart ca ities and great vessels to be measured exactly Lo al build up and disappear ance times to be determined and intracardiac or intravascular shunts to be l ealized which is not possible by the usual peripheral measurement Cali bration is pos ible by me ns of a step-wedge of different depth and/or concentrat on f the radio paque material recorde l simultaneou ly n the same cineangi ogram

The hitherto exi ting observati ns indicate that the recording of ra hopaque dilution curves might provide information of significant clinical nd physiol gic alue

Manufactured by Kipp and Son Company Delft N lands

[illegible] Dr H Heintzen [illegible]

Paul H Heintzen M D Privatdozent
Division of Cardiology
Department of Pediatrics
Christian Albrechts Universitat
Frob lstrasse 15
Kiel Germany

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1 Heintzen P Bunch J and Vietor K W Methoden zur Re i trierung on Kontr tmi tel verdunnung kurven unter Verwendung kom merzieller EKG Geräte und Direktschreiber Z Kreisl aufforsch (In prepar tion)

2 P and Hal brand H Fortl ufende Messung der Kontrastmittel Angiokardiographie Z ts hr

J Verfahren zur tel verdünnungs-

Precordial percussion in cardiac resuscitation

Starting a heart that has suddenly ceased to beat has exercised the imagination and stimulated the interest of medical men since the times of Vesalius, Hunter and Harvey. It was not until 1901, however, that the first successful human resuscitation was achieved (Igelsrud). Since then there have been several reports of successful cardiac resuscitation. In all these the chest had to be opened prior to performing cardiac compression. A new era came into being in 1960 when Kouwenhoven and associates showed that cardiac massage could be performed externally. This extended the scope of cardiac resuscitation, and on both sides of the Atlantic the method was put into use either manually or by mechanical means. Both internal and external cardiac compression, however, are crude methods in that they rely on expelling oxygenated blood from the heart to vital centers by merely squeezing the heart as a whole. Neither achieves a true ventricular contraction and therefore would be expected to be inefficient on purely theoretical grounds. That external cardiac compression achieves forward flow has been demonstrated in a boy on whom it was used during hemodialysis (Lakra and Sawyer 1963). However, measurements of the cardiac output during external massage have yielded disappointingly low values, such that its prolonged use is advised against. In addition, elevation of venous pressure, partly attributable to backward flow from the heart, has been described both in dogs and man.

That a sharp tap to the chest is effective in starting the heart and maintaining its beat was realized by Scherf and Bornemann and Don Michael and associates. An instance of its use in pacing the heart intermittently over a period of 1[illegible] hours has been reported by Don Michael and Stanford. The patient described, who had intermittent complete heart block, developed ventricular standstill and was electrocardiographically monitored during the entire period. It was observed that a sharp blow delivered with the ulnar border of the hand activated the heart, producing one or more ventricular complexes, and that a palpable pulse and recordable blood pressure coincided with the mechanical stimulus. On the same occasion the method was used successfully when epinephrine induced ventricular tachycardia gave place to asystole. Since then the method has been used in several instances of asystole and found to [illegible] at one or more electrocardiographic complexes, some of which are ventricular, [illegible] in [illegible]. Although an electrocardiographic complex [illegible] it does not always produce a palpable pulse and blood pressure, [illegible] it is thought that the prognosis depends on the other factors influencing the outcome in a given case of cardiac resuscitation. However, where it succeeds in producing a pulse it is certainly the method of choice. The difficulty of palpating peripheral pulses due to transmitted pulsation during external cardiac massage has been drawn attention to by Fortal and associates. The method described does not suffer from this disadvantage and one can therefore decide readily whether it is effective. Since the mechanical work involved is much less than that needed in external cardiac massage, the trauma produced is correspondingly less. Experience in cardiac resuscitation has shown that roughly two thirds of all cases of arrest are due to ventricular asystole; hence there is a correspondingly high probability that the method will be successful. The physical effort that is required in external cardiac compression can be considerable, so that the combination of a heavily built patient with an emphysematous chest and a frail medical attendant may render external heart massage impossible. Under these circumstances the method described may well be life saving. Since it is ineffective in ventricular fibrillation, it may be a bedside means of guessing at the cause of the cardiac arrest before an electrocardiogram is obtained. Because of its simplicity, and especially since even a single blow may start up the heart, preventing the need for elaborate measures, it is proposed that it should be tried before external cardiac massage in all cases of cardiac arrest. If successful, as judged by the presence of peripheral pulse and the oscillations of a sphygmomanometer cuff, it can be continued with, thereby reserving external cardiac compression for cases in which the latter procedure has to be used inevitably. Used in conjunction with adequate ventilation and the provision of a satisfactory venous return, where effective it may be efficiently and easily continued with until specialized aid arrives.

T. A. Don Michael, M.B., M.R.C.P. (Lond. & Edin.)
Chief, Department of Internal Medicine
N.I.O.C. University Hospital
Abadan, Iran

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Book reviews

LEHRBUCH DER AUSKULTATION UND PERKUSSION. By Prof. Dr. Med. Klaus Holldack and Dr. Med. Curt Oehme, ed. 5. Stuttgart, 1964, Georg Thieme. 166 pages, 91 illustrations.

The book is profusely illustrated with phonograms taken on 2- to 6-channel recorders simultaneously with ECG or pulse tracings, but the emphasis is on the simple method of auscultation, percussion, palpation, and inspection. This is, however, not a textbook on phonography or hemodynamics, although much detail is given and some recent results of phonocardiographic research are incorporated. Even though auscultation (and percussion) of the thorax (pages 31-114) comprises the major part of the book, examination of the head, neck, peripheral arteries, and abdomen is also included. Thus, in spite of the small volume of 147 pages of text, the content is quite comprehensive although it is on an introductory level. In view of this condensation, the discussion of some topics (for instance, arrhythmias) is superficial, and the book would have gained by even a few references for those students who wish to go into more specific detail. The presentation is excellent both in regard to sequence of topics, style, and the large number of schematic diagrams, and is one of the best primers available. The necessity of a fifth edition after the short interval of [illegible] years and the translation into Italian and Spanish show the popularity of this text in Europe.

DISEASES OF THE HEART AND ARTERIES. By William Evans, M.D., D.Sc., F.R.C.P. (Lond.), Hon. D.Sc. (Wales), Cardiac Department, London Hospital. Baltimore, 1964, Williams & Wilkins Co. 761 pages. Price $ 0.50.

This is an excellent book for [illegible] not only internists and general practitioners but cardiologists as well. Dr. Evans is one of the most prominent cardiologists today. He trained initially with Sir John Parkinson, one of the great cardiologists, [illegible] has reflected this influence to a large extent in this book. The book presents the bedside approach to cardiology with emphasis on the simple and most effective bedside methods of diagnosis and treatment. Evans clearly [illegible] the need for developing a good patient-doctor relationship in history taking. The book is well illustrated and is clearly and concisely written. Many electrocardiograms, phlebograms, teleroentgenograms, and simple diagrams are included. The bibliography is short and [illegible] complete, but it does [illegible] of Dr. Evans' own papers which [illegible] the [illegible] of knowledge and [illegible] for this book. This is good for the book [illegible] Dr. E[illegible] ideas and approaches [illegible] makes readily [illegible] bibliography.

There are a few errors in the book. One, for example, is found in Figure 28 on page 33 in which the QRS complexes in Lead II and III are oriented improperly. Lead II should be oriented along the Lead II axis and Lead III along the Lead III axis of the equilateral triangle. Surely anyone who knows Dr. Evans would expect great emphasis on CR lead; however, this does not reduce the usefulness of the book for those who prefer V lead or any other type of lead system since their differences in clinical medicine are really not that important.

His discussions of pathophysiologic phenomena in heart disease are certainly down to earth. Like this reviewer, he recognizes the need and importance of clarifying them, but he also realizes that from the clinician's point of view much remains to be done, and that in the meantime the physician must administer aid to his patient in spite of this lack of knowledge. Furthermore, even when understood, treatment probably will remain the same. Therefore the [illegible] need to learn the method of the care of the patient and employ them most effectively. For example, on page 581 in his discussion of the mechanism of congestive heart failure he states so correctly: "Fortunately, however, the mechanism of heart failure need not concern us unduly, for the progress of events in the different heart lesions during failure is known, and the exact manner in which they arise is of lesser importance, especially as many of its features are still not understood."

It is good to have this fine book, and clinical medicine will profit considerably from use of it.

THE CORONARY ARTERIES. ARTERIOGRAPHY, MICROANATOMY, AND PATHOGENESIS OF OBLITERATIVE CORONARY ARTERY DISEASE. By William F. M. Fulton, University of Glasgow, Glasgow, Scotland. Springfield, Ill., 1964, Charles C Thomas, Publisher. 354 pages. Price $20.50.

This is a well-written and nicely illustrated book. Included among the illustrations are many stereoscopic figures which can be viewed by means of a viewer provided in a pocket located inside the back cover. The stereoscopy is very good. The author described his method very well so that others may effectively repeat his procedures. The detail of the normal and abnormal circulation of the human heart are shown clearly in the figures.

Among the subjects discussed in this monograph are the normal and abnormal coronary circulation, including anatomy as well as pathology and tomoses, coronary abnormalities in ischemic heart disease, thrombosis and thero-sclerosis, and canalization of thrombotic occlusion. This is a good book which should be of interest to teachers in medicine and cardiology, to investigators concerned with coronary artery

diseases and to practicing internists and cardiologists.

symptomatology and diagnostic measures in arterial angiopathies.

DIE CHIRURGISCHE BEHANDLUNG DER AKUTEN UND CHRONISCHEN ARTERIELLEN VERSCHLÜSSE (The Surgical Treatment of Acute and Chronic Arterial Occlusion.) By A. Senn, Chirurgischen Klinik, Universität Bern, Bern, 1963, Hans Huber, 207 pages, 19 illustrations. Price Fr. DM39.

In this monograph embolic and thrombotic arterial diseases are presented in detail with special reference to the recent Anglo-American literature. The numerous and well arranged statistics from the literature are compared with the results of 287 operations performed by the author. He is in favor of embolectomy even in those patients who are admitted to hospital more than 10 hours after embolism. In 62 per cent of these patients the operation resulted in conservation of the extremity. In peripheral occlusion distal to the iliac artery, lumbar sympathectomy will improve arterial circulation in about 80 per cent of the patients.

In addition to surgical management this book gives the physician a good presentation of the symptomatology and diagnostic measures in arterial angiopathies.

SPATIOCARDIOGRAPHY: TEXTBOOK AND ATLAS. By Prof. Vilem Laufburger, M.D., D.Sc., Member of the Czechoslovak Academy of Sciences, Prague, 1964, Publishing House of the Czechoslovak Academy of Sciences, 189 pages.

This book describes spatial vectorcardiography as practiced in Czechoslovakia. The method and ideas as used by the physicians there are clearly described and well illustrated by diagrams throughout the text and with photographs of spatial vectorcardiograms in an atlas appended at the end of the book. The presentation is supported by mathematical discussions which render the book less interesting to practicing physicians but more valuable to students in the field. The author not only discusses representative records of cardiac disease and the normal but also presents clearly some of the fundamental concepts of vectorcardiography. This is a good book and should be of particular interest to beginners as well as to more experienced investigators in the field.

Announcements

The European Society for Biochemical Pharmacology will organize, in collaboration with the University of Milan, the SECOND INTERNATIONAL SYMPOSIUM ON DRUGS AFFECTING LIPID METABOLISM, to be held in Milan on Sept. 13-15, 1965. The symposium will include long and short lectures by invited speakers and a limited number of free communications.

Requests for information should be directed to Prof. Rodolfo Paoletti, Scientific Secretary, Institute of Pharmacology, University of Milan, Via Andrea del Sarto 21, Milan, Italy.

THE ANNUAL SYMPOSIUM OF THE MEDICAL STAFF OF THE MEMORIAL HOSPITAL OF LONG BEACH, Long Beach, Calif., will be held at the hospital on Wednesday, May 19, 1965.

The program will feature papers by Memorial Hospital staff physicians. Guest speakers will be Marvin Block, M.D., Chairman, A.M.A. Committee on Alcoholism, and Mr. Horace Cotton, professional management consultant and contributing editor of *Medical Economics*.

This symposium is partially supported by a grant from the Farmers and Merchants Bank of Long Beach.

Further information is available from Dr. George N. Trimble, Symposium Secretary, Memorial Hospital of Long Beach, 2801 Atlantic Ave., Long Beach, Calif. 90801.

THE SECOND INTERNATIONAL COURSE ON METHODS FOR LIPID RESEARCH, a NATO Advanced Study Institute, will be held at the University of Milan on Sept. 16-24, 1965. The course will consist of lectures and demonstrations by European and American specialists, with English as the official language. Participation will be limited to 50 postgraduate applicants of any nationality actively interested in lipid research and selected on a competitive basis.

Requests for information should be directed to Prof. Rodolfo Paoletti, Scientific Secretary, Institute of Pharmacology, University of Milan, Via Andrea del Sarto 21, Milan, Italy.

American Heart Journal

An international publication for the study of the circulation

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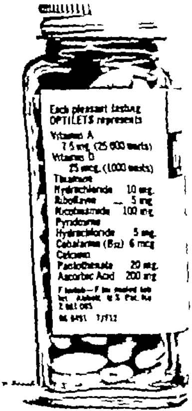
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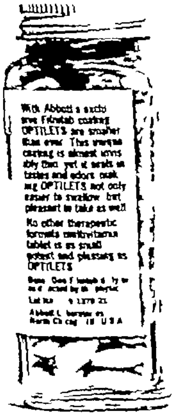
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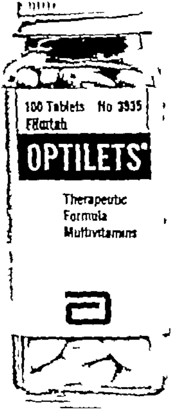
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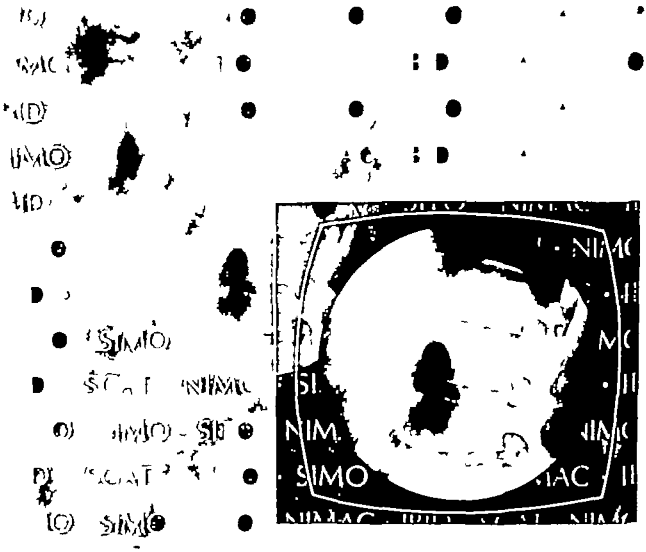
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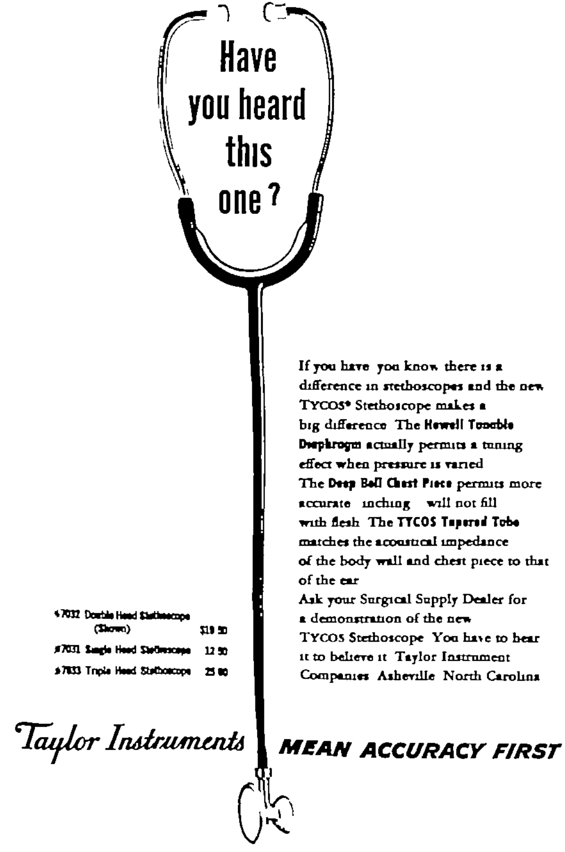


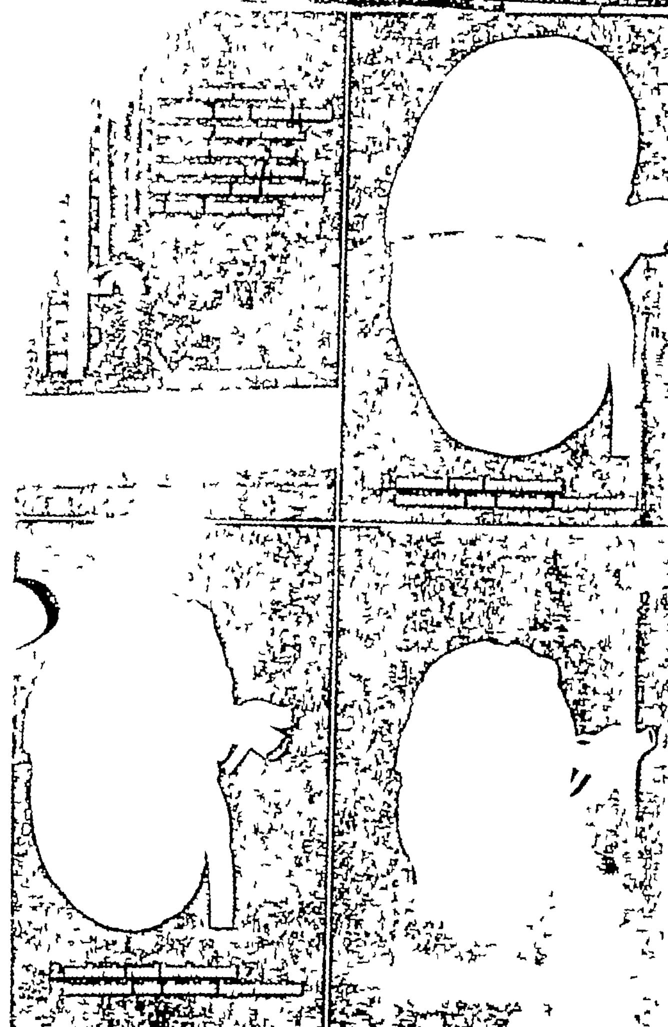
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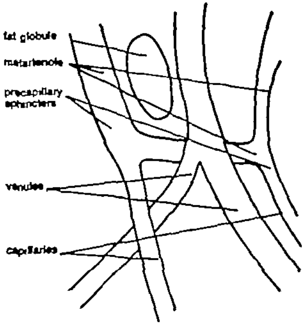



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Photomicrograph Same dog omentum after I V Peritrate (pentaerythritol tetranitrate) There is evidence of increased blood flow and better tissue perfusion experimental dosage form

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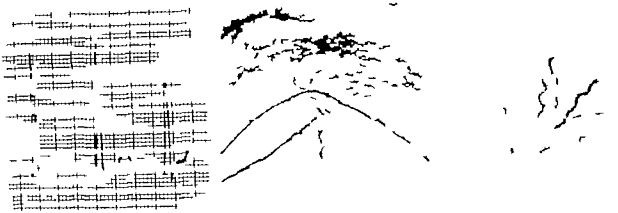
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2 Schumer W Lee D K and Jones B The physiological effect of vasodilators on the omentum of the dog in oligemic shock Angiology in press
3 Data on file in the Medical Department of Warner Chilcott Laboratories 4 Lumb G D and Hardy L B Circulation (Pt II Cardiovascular Surgery) 27 717 1963
5 Sewell W H J A M A 185 234 1963

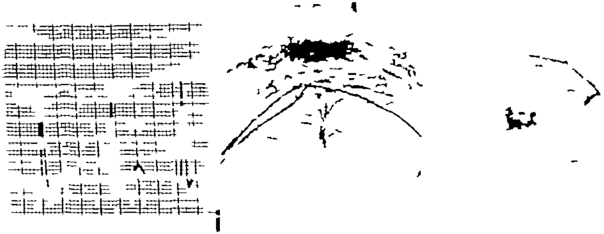
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potassium depletion with thiazide therapy—

Potassium Loss A Corollary of Thiazide Efficiency—The diuretic responses to thiazides also stimulate aldosterone secretion and this makes it inevitable that K loss should occur in rough proportion to efficacy in promoting Na output [1] Potassium depletion may proceed silently before it is signalled by muscular weakness hypokalemia with alkalosis or intestinal distention it may cause electrocardiogram changes[1] or precipitate digitalis toxicity

Potassium Depletion May Be Severe Replacement Often Difficult or Impractical—When urinary excretion of electrolyte is forced by the administration of diuretics large and rapid losses of potassium[2] may be produced This is especially true of the thiazide series which may produce severe potassium depletion

The use of potassium chloride supplements is often restricted because of an unpalatable taste and gastric irritation The enteric coated [KCl] tablets[3] may be irregularly absorbed and may even be excreted in the stools

Indeed there are patients who have large renal losses of potassium[4] and who cannot be controlled by the administration of oral potassium By inhibiting the renal excretion of potassium and enhancing the excretion of sodium spironolactones can keep these patients in much better condition

Aldactazide A Preserves Electrolyte Balance Provides Enhanced Diuretic Action—In a comparative study[4] of hospitalized patients with edema Combined spironolactone and chlorothiazide therapy was significantly more effective than chlorothiazide alone The diuretic response was enhanced and the potassium losing effect of chlorothiazide was counterbalanced by concomitant administration of spironolactone

Spironolactone has been mixed in one pill with hydrochlorothiazide The mixture[1] has little or no significant net effect on K output it may reduce thiazide dose to a point where hyperglycemia or hyperuricemia is negligible In specific situations this mixture may be a drug of choice and it is the single exception to classification of a mixture in this manner

keeps the diastolic down
keeps the patient cooperative

Renese has the demonstrated ability to *keep blood pressure down* with excellent toleration Even long term clinical studies in hypertension [1 5] of resistance to Renese has not been ed Discontinuance of therapy because of effects has been rare In one long term study[1] of 18 months duration 20 patients had been switched to Renese after disappointing experience with several other thiazides In 17 patients followed for the 18 month period the secondary failure phenomenon which had occurred with other thiazides did not occur with polythiazide The 2 mg dose level at which therapy was initiated still adequately met patient requirements Of the three remaining *patients two experienced side effects — one* gastric upset one gout — which subsided within 48 hours after discontinuance of medication one patient was lost to follow up

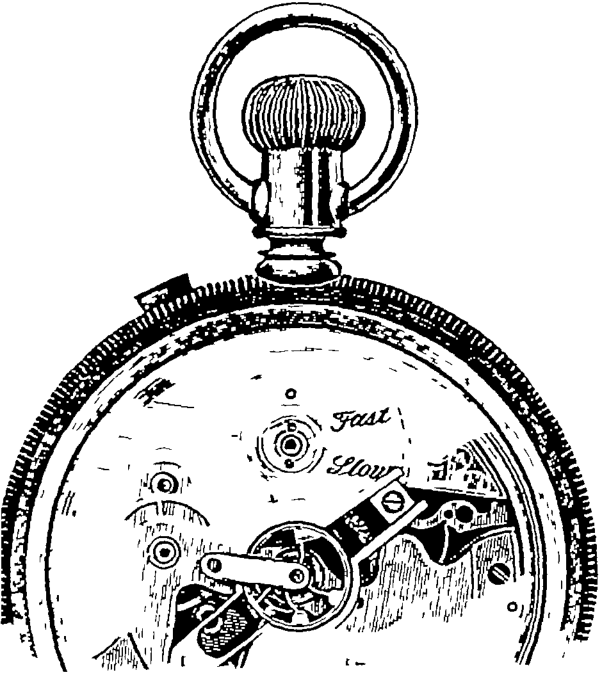
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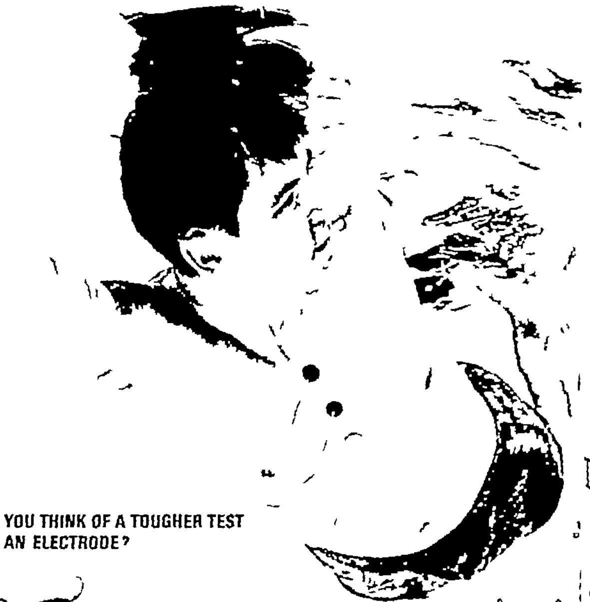




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American Heart Journal

June 1965 Volume 69 Number 6

Editorial

Hyperbaric oxygenation

Potentials and problems

Robert E. Whalen, M.D.
Henry D. McIntosh, M.D.
Durham, N. C.

The recrudescence of the idea that hyperbaric oxygenation might be a useful therapeutic tool demonstrates again that medicine is not immune to the often quoted theme that history repeats itself.[1,2] Three centuries ago the British physician Henshaw first suggested that there might be medical uses for hyperbaric chambers. The idea lay dormant until the early part of the nineteenth century, when three French physicians (Junod of Paris, Tabarie of Montpellier, and Pravaz of Lyon) popularized the use of hyperbaric chambers for the treatment of a variety of afflictions. By the middle of the nineteenth century there was a large number of therapeutic chambers throughout Europe. In 1860 the first therapeutic compression chamber was constructed in North America at Ashawa, Canada. In 1879 Fontaine explored the possible benefits to be gained from surgery under hyperbaric conditions and performed 27 operations in a mobile chamber. Interest in medical applications of hyperbaria waned in the late nineteenth century, although Cunningham constructed and operated large chambers in Kansas City and Cleveland in the nineteen twenties.

Despite Behnke's[3] suggestion in 1940 that the administration of oxygen under high pressure might have clinical application, little further work was done with hyperbaric oxygenation until 10 years ago when Boerema[4] in the Netherlands, Churchill-Davidson[6] in London, and Smith and Illingworth[7] in Scotland began to re-explore the potential usefulness of hyperbaric oxygenation. The preliminary reports from these workers have stirred wide interest and stimulated new studies in centers throughout the world.

The fundamental principles underlying the concept of hyperbaric oxygenation rest upon the laws governing the behavior of gases. Boyle's law states that the pressure of a given quantity of gas whose temperature remains unchanged varies inversely as its volume. As a corollary to this law, it is clear that if the pressure of a gas within a container is to be doubled, twice the quantity of gas must be forced

From the C[illegible] Laboratory, Department of Medicine, Duke University Medical [illegible] supported in part by Grants HE-0[illegible] and HE-0[illegible] from the National [illegible] Heart [illegible] and from the American Heart Association.
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normal subjects. These laboratory observations have been confirmed in cases of carbon monoxide poisoning in patients.[1, 8] The introduction of oxygen with a high partial pressure allows the tissue to obtain necessary oxygen from the store of oxygen physically dissolved in blood. Furthermore, the increased partial pressure of oxygen acts to more rapidly displace the carbon monoxide tightly bound to hemoglobin.

Further projection of these concepts suggests that if there has been partial compromise of arterial flow to an organ sufficient to cause ischemia or necrosis, *what little blood being delivered to the* organ might be so supersaturated with oxygen that necrosis could be prevented. Thus the infarction associated with partial occlusion of a coronary or cerebral vessel might be prevented by hyperbaric oxygenation. The extremity which is ischemic from either chronic or acute arterial insufficiency might be preserved by utilizing hyperbaric oxygenation. Anaerobic infections caused by bacteria which are insensitive to antibiotics but sensitive to oxygen grow in poorly vascularized areas. The increase in oxygen provided by hyperbaric oxygenation may serve to prevent further tissue necrosis and also may be bactericidal to the sensitive bacteria.[14]

The increases in circulating oxygen gained by hyperbaric oxygenation may provide the margin of safety necessary to accomplish palliative procedures in deeply cyanotic infants with congenital heart disease. Since 1962 when Boerema and associates[1] reported the first experience with cardiac surgery during hyperbaric oxygenation, Bernhard and associates[4] have used this technique extensively. Hyperbaric oxygenation may play an even more important role in cardiac surgery when it is combined with extracorporeal circulation. Under hyperbaric conditions the pump-oxygenator system can be miniaturized and priming volumes therefore significantly decreased.

Although tissues receive their primary supply of oxygen from the blood stream, under unusual circumstances oxygen may be delivered by other routes. The skin and mucous membranes of newborn infants may be relatively permeable to high concentrations of oxygen. Significant amounts of oxygen may be delivered to apneic infants through the skin and mucous membranes. The studies of Hutchison and associates[17] in the treatment of apnea neonatorum suggests that this hypothesis is tenable and hyperbaric oxygenation may have a place in the treatment of infants with this condition.

One of the earliest applications of hyperbaric oxygenation was based on the observation that malignant tissues are more sensitive to radiation therapy when exposed to increased concentrations of oxygen. Churchill-Davidson,[6] who pioneered *in this work, believes that hyperbaric* oxygenation has a valid place in radiation therapy for certain malignancies.

The initiation of a hyperbaric oxygenation program is not without significant problems. These problems include the actual mechanics of acquiring, equipping, and staffing a hyperbaric unit, as well as significant potential health hazards to patients and personnel subjected to hyperbaric conditions. The cost of a chamber and necessary auxiliary equipment may rapidly reach almost astronomical sums.

The operation of instruments designed to aid in the care and study of patients becomes more complex under hyperbaric conditions. Instruments containing vacuum tubes and other closed containers must be pretested to determine whether their components can withstand pressures of 2 to 6 atmospheres (up to 88 pounds per square inch). Oils frequently used for lubrication may be a fire hazard or may become useless during hyperbaric exposure because of the formation of bubbles in them. Much of the electrical equipment commonly used in the care and study of patients cannot be used within a hyperbaric chamber because of the danger of setting a fire in the oxygen-enriched atmosphere present during hyperbaric exposures. Brown and Smith[18] have emphasized the extensive precautions necessary to prevent the catastrophic effects of a fire under hyperbaric conditions.

Aside from problems of instrumentation, hyperbaric oxygenation may provide certain health hazards for patients and for personnel. Personnel who cannot easily open their Eustachian tubes and thus

3 atmospheres. Donald[4] has emphasized that there is a wide variation in susceptibility to acute oxygen intoxication among individuals. Furthermore, there is a striking day-to-day variation in the susceptibility of the same individual. At the present time it appears that interrupted programs of oxygen exposure while under hyperbaric conditions may prevent the signs of acute oxygen intoxication.

An accurate appraisal of the efficacy of hyperbaric oxygenation in the treatment of various disease states is impossible at this time. The present enthusiasm over the therapeutic application of hyperbaric oxygenation must be weighed against the earlier history of enthusiasm and eventual disillusionment associated with this technique. Much of the final evaluation of hyperbaric oxygenation will depend upon estimations of the clinical improvement of patients subjected to this form of therapy. Such evaluations are often unintentionally biased, and large numbers will have to be accumulated before trends may become apparent. It would appear, however, that hyperbaric oxygenation may be of benefit in the treatment of carbon monoxide intoxication and certain anaerobic infections. It may gain a place in the surgical management of certain forms of congenital heart disease, the treatment of asphyxia neonatorum, and the radiation therapy of certain malignancies. Its place in the treatment of peripheral vascular disease, shock, myocardial infarction, and cerebral vascular disease is still to be explored.

The treatment of occlusive vascular disease in the heart, the brain, and the extremities presents certain inherent problems which may be insurmountable or may require unique solutions. Brown and associates have reviewed the theoretical problems involved in the delivery of adequate amounts of oxygen to ischemic organs. When there is no flow to a region and collateral circulation is inadequate, no increase in circulating oxygen will prevent death of tissue. The final solution to the treatment of occlusive vascular disease may depend on the combination of hyperbaric oxygenation and a means other than the circulatory system of delivering oxygen to tissue. The work of Hutchison and associates[17] suggests that under unusual circumstances skin and mucous membranes may afford an avenue for the delivery of oxygen to tissues. It is conceivable that the effective treatment of occlusive vascular disease will depend on further exploration of nonvascular routes for the delivery of oxygen to tissue.

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Clinical communications

The effects of guanethidine and of alpha-methyldopa on the digital circulation in hypertension

*Milton Mendlowitz, M.D.**
Nosrat E. Naftchi, M.S.
Robert L. Wolf, M.D.
Stanley E. Gitlow, M.D.
New York, N. Y.

Evaluation of the mechanism of action of various antihypertensive drugs is fraught with several difficulties. For example, the results in animal investigations may be different from animal to animal, including man, and in the same animal the effect of the drug may change with the length of time that the drug is administered. Also, in man the mechanism may be different in the upright and in the recumbent positions and may be affected by such factors as climate, race, heredity, emotion, and diet.

The exact mechanism of the antihypertensive effect of two currently employed drugs, guanethidine and α-methyldopa, is still imperfectly understood. In animals it can be shown that both drugs[1-4] deplete stores of catecholamines in the heart as well as in other tissues. In contrast with reserpine, however, guanethidine does not increase the release of norepinephrine (NE) from isolated storage granules. It is believed by some workers that guanethidine releases NE by acting on a cholinergic trigger mechanism. When given intravenously, it releases sufficient NE to produce a transient rise in venous blood catecholamines as well as a transient increase in heart rate, blood pressure, cardiac output, and blood volume. The central nervous system, however, remains relatively unaffected by both guanethidine and α-methyldopa because of the failure of these drugs to cross the blood-brain barrier to any significant extent. There is, however, some difference of opinion on this point. Increased responsiveness to exogenously administered NE and decreased responsiveness to exogenous tyramine are attributed to depletion of NE stores in these animals. With reference to guanethidine, however, vasodilatation seems to take place sooner than significant depletion of NE can be documented, and some workers believe that the drug produces some direct vasodilatation.

The antihypertensive effect of α-methyldopa is thought not to be attributable to interference with NE synthesis because of decarboxylase inhibition. Although the drug has this effect, other even more potent

From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.
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*Address: The Mount Sinai Hospital, [illegible] New York, N. Y. 10029

decarboxylase inhibitors, for example, are not antihypertensive. It is now believed that a metabolite of α-methyldopa, α-methylnorepinephrine, which is relatively nonpressor, competes for binding sites both within the stores and on the surface of smooth and heart muscle cells (α receptors) and is responsible for depletion of stores of NE and for increased reactivity to NE in animals.[illegible]

In man, both drugs[illegible] produce a decrease in blood pressure in the upright position. With respect to guanethidine, this is associated with a decrease in cardiac output, glomerular filtration rate, and renal blood flow, although there is little change in blood pressure or cardiac output in the supine position. As time goes on, however, the adverse effects on renal function tend to return toward normal. Alpha methyldopa, on the other hand, does produce a decrease in blood pressure in the supine position. Cardiac output, glomerular filtration rate, and renal blood flow are not decreased. Furthermore, either guanethidine or α-methyldopa given alone may produce retention of sodium and edema manifested a few weeks after the start of therapy. This effect is uncommon, however, if either drug is given together with a thiazide diuretic. Tissue depletion of catecholamines by these drugs has not been documented in man, although there is some evidence of increased reactivity to NE and decreased pressure response to tyramine, at least with reference to guanethidine. Some observers, however, were unable to demonstrate a decreased response to tyramine after acute as well as long-term administration of guanethidine. It must be emphasized that most studies on the effects of drugs in man are acute studies rarely exceeding 1 week of drug administration. It is well known that long-term antihypertensive effects of some drugs may be quite different from their initial effects.

Methods

With these reservations in mind, the effects of the two antihypertensive drugs were compared in two groups of patients with essential hypertension. Each group consisted of 15 subjects. In one group, guanethidine (25 mg. twice a day) was administered orally to each subject, and in the other group α-methyldopa (250 mg. three times a day) was given. In the guanethidine group, 6 patients were treated for 2 weeks, 1 for 3 weeks, and 8 for 4 weeks. In the α-methyldopa group, 6 patients were treated for 2 weeks, 2 for 3 weeks, 6 for 4 weeks, and 1 for 6 weeks. Circulatory studies, including the measurement of brachial and digital blood pressure, digital blood flow, radius equivalent, and vascular reactivity to NE, were carried out in both groups.

Each subject in both groups was tested twice under the same conditions, prior to and after administration of the drugs. Each test of vascular reactivity prior to and after administration of the drug was carried out with the patient in the supine position and under three sets of conditions:* (1) Phase B, at rest under standardized conditions (room temperature 26 to 29° C.); (2) Phase A, after vasodilatation produced by indirect heating of the patient with a cradle baker over the trunk until positive heat balance was attained, as manifested by copious diaphoresis. At this point, 0.6 mg. per kilogram of a ganglion-blocking drug, 2,6-dimethyl-1-diethyl piperidinium bromide (SC 1950), was administered intravenously; (3) Phase C, after vasodilatation plus NE, consisting of keeping conditions in Phase A constant, together with infusion of NE and additional SC 1950. The rate of infusion was so regulated by an infusion pump as to raise the brachial blood pressure to about the same level as, or 20 mm. Hg above, the starting pressure (pressure in Phase B). The infusion fluid was 5 per cent dextrose in water and contained 24 μg. per cubic centimeter of l-norepinephrine bitartrate and 100 μg. per cubic centimeter of SC 1950.

In each phase, digital blood flow was measured calorimetrically, and systolic and diastolic digital pressures were measured by a Gaertner capsule.[illegible] Mean pressure was calculated by adding one-third of the pulse pressure to the diastolic

*[illegible]

pressure. From the mean digital blood pressure thus obtained, a calculated venous pressure correction was subtracted. The radius equivalent of the digital circulation was computed from the digital blood flow and effective mean digital blood pressure by using Poiseuille's law. The length factor for the digital circulation was calculated and considered to be constant and was corrected for variations in finger tip size. In the constricted states, Phases B and C, corrections were made for critical closing pressure and/or apparent change in blood viscosity. The work of vasoconstriction for the digital circulation was estimated from the following formula[illegible]:

$$w = 19.5\,P_1(r_1 - r_2) - \frac{16.1\,P_1^2(r_1^4 - r_2^4)}{Q_1}$$

in which w is work in ergs, P_1 is effective mean pressure and Q_1 is blood flow in the dilated state (Phase A), r_1 is radius equivalent during vasodilatation (Phase A), r_2 is radius equivalent in the resting state (Phase B), and r_3 is the radius equivalent during vasoconstriction brought about by NE infusion (Phase C) replacing r_2 in the formula when the work of vasoconstriction produced by NE is measured. From the work thus estimated and the rate of infusion of NE, the work per microgram of NE per minute was calculated.

Results

Guanethidine caused an increase in reactivity to NE beyond the 99 per cent fiducial limit. The drug produced no vasodilatation in the digit in the resting recumbent position (Phase B) (Table I). It did, however, cause some increase in the digital blood pressure after vasodilatation (Phase A) with no concomitant change in blood flow, indicating a slight but significant decrease in radius equivalent in the dilated state (Phase A). Alpha methyldopa, in contrast to guanethidine, produced a significant vasodilatation in the recumbent resting state, as manifested by a rise in resting blood flow and radius equivalent and hence a decrease in the work of vasoconstriction from the dilated to the resting state (Phase B). The change in radius equivalent was not associated with any significant change in digital blood pressure (Table II). Only the supine resting brachial systolic blood pressure was significantly reduced at the 95 per cent fiducial limit by α methyldopa. In addition, α methyldopa produced a statistically significant ($p < 0.01$) increase in reactivity to NE similar to that produced by guanethidine. In 2 patients in the guanethidine group and in 2 patients in the α methyldopa group, no significant increase in reactivity was produced by the drug. However, in 1 of the guanethidine patients and in 1 of the α methyldopa patients the drug had been administered for only 2 weeks. In 1 other patient, α methyldopa had been given for 4 weeks, whereas in another case, although guanethidine was administered for 4 weeks, the patient reported irregularity in taking the drug. In 5 other patients treated with guanethidine for only 2 weeks, however, and in 5 patients treated with α methyldopa for 2 weeks, reactivity was significantly increased, and in all the other patients treated for more than 2 weeks, with the exception of the 2 cases cited, responsiveness was always increased.

Discussion

The increase in reactivity can probably be attributed to depletion of NE stores by the drugs. NE depletion brought about by α methyldopa, as has already been indicated, is not attributable to decarboxylase inhibition per se but is probably produced by one of the drug's metabolites, α methylnorepinephrine.[illegible] Our findings confirm the vasodilating and blood pressure reducing effect of α methyldopa in the supine position[illegible] in addition to its known postural hypotensive effect. It is well known that the initial blood pressure lowering effect of guanethidine is mainly attributable to its interference with maintenance of the blood pressure when the patient is in the erect position. In our experiments all measurements of pressure were carried out with the patient in the supine position. This probably accounts for the failure to find a statistically significant change in resting supine blood pressure in patients treated with guanethidine. It is also possible that other mechanisms for the reduction of blood pressure

Table I The effect of guanethidine on the digital circulation in hypertension

	Phase	Before Mean	± SD	After Mean	± SD	S E d	p
Brachial blood pressure systolic (mm Hg)	A	164	29	175	28	10	< 0 4
	B	185	28	171	32	11	< 0 3
	C	200	22	237	33	10	<10 ²
Brachial blood pressure diastolic (mm Hg)	A	87	14	100	11	4 5	<10 ²
	B	104	11	94	11	4 0	< 0 02
	C	112	15	120	10	4 7	< 0 09
Digital blood pressure systolic (mm Hg)	A	124	23	158	6	8 8	<10 ²
	B	164	29	155	30	11	< 0 5
	C	183	24	216	42	12	<10
Digital blood pressure diastolic (mm Hg)	A	77	14	86	10	4 4	< 0 02
	B	91	12	87	11	4 4	< 0 06
	C	102	12	110	8 9	3 8	< 0 05
Effective mean digital blood pressure (mm Hg)	A	87	17	102	16	5 9	<10 ²
	B	110	17	102	17	6 2	< 0 3
	C	119	13	136	18	5 7	<10
Digital blood flow (cm ³/cm ² skin/min)	A	0 26	0 070	0 25	0 061	0 023	< 0 5
	B	0 14	0 087	0 10	0 075	0 029	< 0 2
	C	0 22	0 071	0 18	0 084	0 079	< 0 2
Radius equivalent (10 cm)	A	2 8	0 24	2 6	0 22	0 085	< 0 07
	B	2 4	0 39	2 3	0 30	0 13	< 0 5
	C	2 5	0 32	2 3	0 28	0 11	< 0 07
Work of vasoconstriction (10⁸ ergs)	B	2 9	2 3	2 3	1 8	0 75	< 0 5
	C	1 4	0 9	1 7	0 85	0 32	< 0 03
Rate of NE infusion (μg/min)	C	8 4	2 9	6 3	1 5	0 82	< 0 07
Work of vasoconstriction per μg NE per min (10⁸ ergs)	C	0 163	0 063	0 267	0 10	0 031	<10 ⁴

A After vasodilatation B Before vasodilatation C After vasodilatation during infusion of NE
*Standard deviation
**Standard error of the difference
***Probability that the difference is due to chance

supervene when the drugs are administered over a longer period of time than in these studies[14,73] The slight increase in blood pressure in the vasodilated state (Phase A) as well as the slight decrease in vascular caliber found after the administration of guanethidine for from 2 to 4 weeks may be attributable to edema of the walls of the blood vessels Theoretically this effect could be prevented by the simultaneous administration of a diuretic

Summary

1 The reactions of the digital circulation to drugs were compared in two groups of 15 hypertensive subjects each In one group the patients received α methyldopa (750 mg daily) for 2 to 8 weeks and in the other they received guanethidine (50 mg daily) for 2 to 4 weeks

2 Digital circulatory studies in the supine position involving measurements of flow pressure radius equivalent and

activity to NE in both groups was probably attributable to depletion of NE from tissue stores by the drugs

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doctor or nurse was nearby at the onset of cardiac arrest and was able to institute external cardiac massage and give the appropriate alarm. For these patients the initial attempts at defibrillation were undertaken with a mobile resuscitation trolley taken to the patient before he was transferred to the intensive care unit.

Methods

External cardiac massage was performed as described by Kouwenhoven and associates[1] and was continued until there was an adequate spontaneous circulation or until the attempt at resuscitation was abandoned. To facilitate massage the patient was placed on a firm base, e.g. fracture boards or the floor. The adequacy of external cardiac massage was checked frequently by palpation of the femoral pulses and observation of the diameter of the pupils. In some patients external cardiac massage was effective to the point at which the patient regained consciousness and required intravenous sodium amylobarbitone sedation in order to allow external cardiac massage to continue.

Ventilation with oxygen was given by endotracheal tube. However, until intubation an oral airway with a R.M. Resuscitator[24] was used. This delivers oxygen to a face mask at a flow rate of 60 liters per minute and has an intermittent positive pressure valve which is manually cycled. A relief valve set at 40 mm. Hg prevents excessive intrapulmonary pressure.

Metabolic acidosis due to anaerobic glycolysis follows circulatory arrest. Sodium bicarbonate will correct this acidosis, improve myocardial function, and may decrease the incidence of arrhythmias after resuscitation. Thus an intravenous infusion of 100 to 200 ml. of an 8.4 per cent solution of sodium bicarbonate (1 mEq. per milliliter) was begun as soon as possible.

In those patients who were not being monitored at the time of cardiac arrest an electrocardiogram was obtained rapidly by means of needle electrodes. Four sterilized Luer Lok needles were kept in readiness on the mobile resuscitation trolley and in the intensive care room as were electrocardiograph cables modified by attachment of Luer Lok fittings to their terminals. A needle was passed into each of the patient's limbs and the electrocardiograph cable connected. This obviates the time-consuming practice of applying electrode jelly, standard electrodes, and straps. The electrocardiogram then dictated the nature of further treatment depending on whether cardiac arrest was due to ventricular fibrillation or asystole. After successful resuscitation, electrocardiographic monitoring was continued until the cardiac rhythm was stable and the patient's condition satisfactory.

Ventricular fibrillation was treated by prompt external electrical countershock, A.C. or D.C.; cardiac massage and ventilation were continued up to the moment of electrical discharge. If, after administration of 100 to 150 mEq. of sodium bicarbonate intravenously, ventricular fibrillation remained refractory to defibrillation, then up to 750 mg. of procaine amide was given intravenously, after which electrical countershock was repeated. If sustained asystole or slow idioventricular rhythm with an inadequate circulation followed defibrillation, external cardiac massage was continued and isoprenaline hydrochloride, 0.2 mg., and/or 5 to 10 ml. of 10 per cent calcium gluconate was given intravenously.

Asystole was treated by external cardiac massage and infusion of 100 to 150 mEq. of sodium bicarbonate. When asystole was persistent, isoprenaline hydrochloride, 0.2 mg., and/or 5 to 10 ml. of 10 per cent calcium gluconate was given intravenously. If asystole developed in patients in whom complete atrioventricular block complicated the acute myocardial infarction, the external electrical pacemaker was used. Intracardiac injection was used as a last resort in cases of asystole because of the dangers of hemopericardium and damage to the coronary vessels.

After successful resuscitation, procaine amide, 250 mg. every 6 hours, was given intramuscularly as prophylaxis against recurrent ventricular fibrillation, and the patient was given sodium amylobarbitone, 100 to 150 mg. orally every 6 hours. Hypotension that followed resuscitation was treated with intramuscular metaraminol

[illegible]

if this was inadequate intravenous noradrenaline was used Complete atrioventricular block after resuscitation was treated with 300 mg of hydrocortisone intravenously together with intramuscular or intravenous isoprenaline hydrochloride in doses sufficient to maintain an adequate ventricular rate When prolonged ventricular or supraventricular tachycardia followed resuscitation synchronized D C countershock was used Respiratory embarrassment due to damage to the chest wall from external cardiac massage was treated by early tracheostomy If spontaneous ventilation was inadequate respiration was controlled through the use of an intermittent positive negative pressure respirator (Bird Mark VIII)

The intensive-care ward was staffed by nursing sisters who were instructed in the electrocardiographic recognition of cardiac arrhythmias and with increasing experience they rapidly became proficient They were trained in the methods of external cardiac massage and artificial respiration with an oral airway face mask and bag or an R M Resuscitator They were instructed in the operation of cardiographic monitoring oscilloscopes electrocardiographic recorders external electrical defibrillators external electrical pacemakers and the Bird Mark VIII respirator When cardiac arrest occurred in a patient in the intensive-care ward these sisters initiated external cardiac massage and artificial respiration and summoned the medical staff

Terminology

Classification of patients Patients were classified into three groups depending upon their clinical condition prior to the onset of cardiac arrest A modification of the system of Freis and associates[12] was used Infarction was considered to be *mild* if there was no evidence of cardiac failure apart from a transient rise in the jugular venous pressure *Severe* infarction was present if there was definite evidence of circulatory embarrassment including prostration hypotension or evidence of cardiac failure *Cardiogenic shock* was considered to be present when the criteria of Binder and associates[13] for severe shock were satisfied These include a systolic arterial pressure below 80 mm Hg pallor cyanosis a sweating cold skin oliguria and failure to improve within half an hour after relief of pain and the administration of oxygen

Success and survival Resuscitation was considered to be successful when a patient who had been clinically dead was resuscitated such that there was a return of spontaneous circulation and he had spoken Survival beyond 6 weeks from the last attempt at resuscitation is called *long term survival* whereas *limited survival* is for a lesser period

Results

Of the 38 patients who had cardiac arrest after myocardial infarction 8 were classified as having suffered mild infarction 22 had severe infarction and 8 had cardiogenic shock In all 8 patients with mild infarction cardiac arrest was due to ventricular fibrillation Of the 22 patients with severe infarction 16 had ventricular fibrillation and 6 had asystole In all 8 patients with cardiogenic shock cardiac arrest was due to asystole The results of the attempts at resuscitation in the 38 patients are shown in Table I

Mild infarction Of the 8 patients who were considered to have mild myocardial infarction resuscitation was successful in 7 and all of these are long term survivors All 7 are active and have resumed their normal pattern of life Survival to date for this group has been from 2 to 18 months The following two cases are representative

Case 1 A 66 year-old retired accountant gave a history of 2 hours of crushing retrosternal chest pain which radiated to the back and down both arms The blood pressure was 130 mm Hg systolic and apart from sweating there were no abnormal clinical signs A 12 lead electrocardiogram was normal

Thirty minutes later sudden collapse occurred The electrocardiogram showed ventricular fibrillation External cardiac massage was begun immediately and an endotracheal tube passed Spontaneous respiration returned and the patient began to struggle A single 450 volt 0 1-second shock from an A C defibrillator resulted in idioventricular rhythm but ventricular fibrillation rapidly recurred Because of the difficulty in establishing a functioning intravenous infusion in this agitated patient 300 mg of sodium amylobarbitone was given intravenously before an infusion of 140 mEq of sodium bicarbonate could be begun

During the next 35 minutes the patient was given an additional 6 shocks each of 450 volts

oncentrations of Rb^{86} in arterial blood circulating in the left ventricular cavity

The results of this study suggest that the slightly higher left ventricular endocardial clearance of intravenously infused Rb^{86} found by Love and Burch under normal conditions of coronary perfusion was due to uptake directly from the ventricular cavity. However, their more significant finding of an enhanced endocardial clearance of Rb^{86} after the administration of norepinephrine and Pitressin may not be explicable on this basis, although this possibility cannot be excluded. The results of the present study indicate that high concentrations of Rb^{86} must be eliminated from arterial blood circulating in the left ventricular cavity before meaningful interpretation can be given to differences in uptake and clearance between the endocardial and epicardial halves of the myocardium.

Summary

A difference in uptake and clearance of intravenously infused $Rb^{86}Cl$ between the endocardial and epicardial halves of the normally beating left ventricle of the dog has been shown. The higher endocardial clearance was due to the uptake of isotope directly from the left ventricular cavity rather than to increased forward coronary flow to the endocardium. When the ventricular source of isotope was eliminated, the uptake of Rb^{86} by the endocardium was less than that by the epicardium and was consistent with decreased forward coronary flow in the inner layers of the left ventricular myocardium under normal pressure-flow conditions.

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Uptake of I^{131}-tagged sodium iodide, triiodothyronine, and thyroxine by experimental myocardial infarcts in dogs

F. Dreyfuss, M.D.
S. Rogel, M.D.
S. Guttman, B.Sc.
J. Gross, M.D., Ph.D.
Jerusalem, Israel

The observation of an increased isotope activity over the precordial area in patients with myocardial infarction after the administration of radioiodine prompted this experimental study.[1] A series of experiments was designed in which myocardial infarcts were produced in dogs by coronary ligation and the uptakes of I^{131} labeled sodium iodide, triiodothyronine (T_3) and thyroxine (T_4) were investigated. At the same time the uptake was determined in the healing chest wound that had resulted from the thoracotomy, as a further measure of the entry of these substances into necrotic and/or healing muscle tissues.

Material and methods

The experiments were carried out in 17 mongrel dogs weighing between 3.5 and 10 kilograms. The dogs were anesthetized with sodium thiopentone, 35 mg. per kilogram of body weight, administered intraperitoneally. Artificial respiration was maintained by a mechanical respirator. Left anterolateral thoracotomy was performed in the fifth intercostal space and the pericardium was opened longitudinally anterior to the phrenic nerve. In 14 dogs the anterior descending branch of the left coronary artery was then ligated just below or just above the take-off of its first large branch. This site was chosen according to the vascularization pattern of the anterior surface of the left ventricle and the apex in each individual animal. In a number of experiments additional branches of the coronary arteries had to be ligated in order to produce immediate discoloration of the myocardium below the ligation. The pericardium was then loosely attached, the chest wall was closed, and negative intrapleural pressure was created through an intercostal drain. All dogs developed marked necrosis of the left ventricular wall localized in the anterior lower third of the whole apex, of part of the posterior wall, and of the lower portion of the interventricular septum. In 3 dogs the same procedure was carried out, but with sham ligation of the coronary artery.

Two days after the operation, 6 dogs were given NaI^{131} in doses ranging from

With the technical assistance of Mr. Samuel W[illegible].
From the Department of Experimental Medicine and Cancer Research, Hebrew University Hadassah Medical School, and the Departments of Internal Medicine A and B, Hadassah University Hospital, Jerusalem, Israel.
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17 to 44 μC per kilogram of body weight. The animals which were given T_3 (5 dogs) and T_4 (6 dogs) received the injections 3 days after surgery in doses of 0.5 μg per kilogram of body weight.

Usually 1 day, but also up to 3 days after the administration of the radioactive material, the dogs were again anesthetized with sodium thiopentone. After the dogs had been heparinized, they were bled to death and autopsy was performed immediately. A piece of pectoral muscle was taken for examination from the incised left chest wall and from the untouched right wall. A sample of whole blood was also taken. The heart was removed and samples of myocardium were taken from the infarcted and noninfarcted areas of the left ventricle and also from the right ventricle. These samples as well as those from both pectoral muscles were weighed and their radioactivity was counted in a well type of gamma ray spectrometer. The reliable error of the counts was within 3 per cent.

Plasma protein bound iodine (PBI) was determined by precipitation with an equal volume of 15 per cent trichloracetic acid solution containing 1 per cent potassium iodide and the precipitate was washed twice with 5 per cent trichloracetic acid solution. The tissues were frozen with dry ice, powdered in a mortar in the frozen state and taken up in 1 per cent ammonia solution. The aliquot was neutralized and used for the determination of PBI as outlined above.

In 1 dog the tissues were also extracted with n-butanol at pH 1 with the butanol extract concentrated and chromatographed in butanol-dioxan-ammonia by the ascending technique. The chromatogram strip was cut into horizontal strips of 1 cm width. These were counted and the graphs of the distribution of radioactivity in the strips were drawn (Fig. 2).

Results

Fig. 1 shows the mean concentration of both total and protein bound radioactivity in the heart muscle in all four types of experiments. It may be seen that in all cases there appears to be a greater concentration in the infarcted tissues than in the normal heart muscle. The biggest difference is evident after treatment with thyroxine.

The significance of these differences is analyzed in Table I.

In order to correct for the varying rates of disappearance of the injected material from the circulation, a parameter called

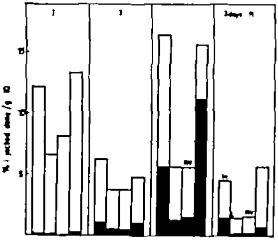


Fig. 1. The concentration of radioactivity in infarcted and normal heart muscle after intravenous NaI131, I131 triiodothyronine and I131 thyroxine. In, Infarcted left ventricle; LI, Normal left ventricle; RI, Normal right ventricle; P, Plasma.

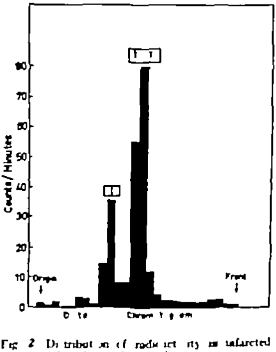


Fig. 2. Distribution of radioactivity in infarcted left ventricle 4 hours after I131 thyroxine.

Table I. A comparison of the spaces for iodide, triiodothyronine and thyroxine in normal and infarced heart muscle expressed as Mean ± S.E.

	Infarcted left ventricle (ml./Gm.)	Normal left ventricle (ml./Gm.)	Normal right ventricle (ml./Gm.)	Combined normal values (ml./Gm.)	Significance of infarcted vs. normal	Ratio of infarcted to normal
Sodium iodide (3)						
Operated	0.70 ± 0.037	0.43 ± 0.035	0.41 ± 0.059	0.42 ± 0.05	$p < 0.001$	1.7
Sham-operated	0.42 ± 0.036	0.41 ± 0.024	0.39 (2)			
Triiodothyronine (5)						
T_3 space	0.79 ± 0.073	0.54 ± 0.086	0.52 ± 0.098	0.53 ± 0.062	$p < 0.02$	1.5
Iodide space	1.41 ± 0.164*	0.94 ± 0.134	0.97 ± 0.108	0.95 ± 0.091	$p < 0.05$	1.5
Thyroxine						
1 day (4)						
T_4 space	0.55 ± 0.070	0.14 ± 0.066*	0.16 ± 0.034	0.15 ± 0.033	$p < 0.001$	3.3
Iodide space	1.90 ± 0.462	0.88 ± 0.278	0.79 ± 0.128	0.81 ± 0.122	$p < 0.05$	2.3
3 days (1)						
T_4 space	2.6	0.33	0.32	—	—	7.9
Iodide space	0.43	0.21	0.72	—	—	2.0

*[illegible]

a space was calculated according to the following formula

$$\frac{\text{Concentration I}^{131}\text{ in tissue (counts/min./Gm.)}}{\text{Concentration I}^{131}\text{ in plasma (counts/min./ml.)}} = \text{ml./Gm.}$$

This is illustrated by the calculation of the iodide space in all samples of normal heart muscle taken from the sham-operated animals and from the normal left and right ventricles. These show a consistent value varying between 0.39 and 0.42 ml. per gram. In the case of the experiments with T_3 and T_4 the protein bound iodine values were used for the calculation of the spaces for the respective iodoamino acids and the nonprotein bound iodine values were used to calculate the iodide space. Chromatographic analysis of the various fractions after treatment with T_4 (Fig. 2) indicated that the major organic component present as protein bound iodine was predominantly T_4. This justified the use of the PBI values for calculating the T_4 space and by analogy the T_3 space.

The data in Table I show that 24 hours after the administration of radioactive iodide the iodide space of infarcted heart muscle is 1.7 times larger than that of normal myocardium. Similarly, after radioactive triiodothyronine the T_3 space of the infarct is 1.5 times that of normal heart muscle. The increase is more marked after the administration of radiothyroxine. Thus at 24 hours the T_4 space of infarcted muscle is 3.3 times greater than that of normal myocardium and there appears to be a further increase at 3 days. These differences are highly significant statistically except in the 3 day thyroxine experiment in which there were insufficient data for analysis.

It may be noted that in both experiments with T_3 and T_4 the iodide space in the normal tissue and in the infarcted tissue exceeds that shown after the administration of NaI^{131}.

The distribution of radioactivity in the pectoral muscle is shown in Fig. 3. After sodium iodide and thyroxine there are somewhat greater concentrations in the incised than in the normal muscle. No difference is seen after the administration of T_3. When the various spaces are c

Table II A comparison of the spaces for iodide triiodothyronine and thyroxine in normal and incised pectoral muscle

	Incised muscle (ml Gm)	*Normal muscl (ml /Gm)*	*Significance of difference*	*Ratio of infarcted to normal*
Iodide pace (6)	0 55 ± 0 05	0 24 ± 0 074	p < 0 001	2 3
Triiodothyronine (4)				
T pace	0 38 ± 0 075	0 45 ± 0 145	NS	0 8
Iodide space	0 97 ± 0 103	0 85 ± 0 185	NS	1 1
Thyroxine (4)				
1 day				
T space	0 2 ± 0 134	0 10 ± 0 016	NS	2 7
Iodide pace	1 18 ± 0 155	0 48 ± 0 116	p < 0 02	2 5
3 days (2)				
T space	0 65	0 23	—	2 8
Iodide space	0 59	0 11	—	5 4

pared (Table II) only the iodide space is significantly higher in the damaged skeletal muscle A similar comparison in the experiments with I and T shows no significant differences in the iodoaminoacid spaces Only the iodide space 1 day after the administration of T_4 is greater in the incised than in the normal muscle

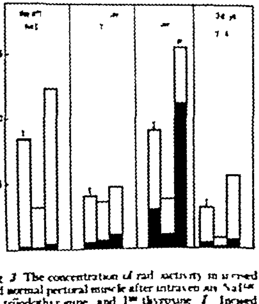


Fig 3 The concentration of radioactivity in incised and normal pectoral muscle after intravenous NaI[131] I[131] triiodothyronine and I[131] thyroxine *I* Incised pectoral muscle N Normal pectoral muscle *P* Plasma

Discussion

The infarcted heart muscle of the dog takes up all of the three labeled substances investigated in higher concentrations than does the noninfarcted myocardium The results after the administration of iodide confirm the findings of Lourvanij and Silberstein The highest concentrations are obtained when radiothyroxine is given and at 72 hours after administration the concentration of PBI in the damaged tissue exceeds that in the plasma A chromatogram taken from an extract of the infarct was identifiable as that of T_4 The muscles of the chest wall incised for the experimental procedure similarly showed an increased concentration of isotope as compared with the intact pectoral muscle of the right side

It has been shown that 48 hours or later after the administration of NaI[131] to patients or dogs with myocardial infarcts there are significantly higher concentrations of radioactivity in the infarcted area At 48 hours or later after the administration of sodium iodide there would be significant biosynthesis of endogenous T_4 thus contributing to a greater difference between the uptake of the damaged myocardium and that of the normal myocardium The failure of Dreyfuss and associates to detect significant differences within 24

hours after the administration of iodide with the isotope still circulating largely in the inorganic form would indicate that the difference in iodide space such as was demonstrated in the present experiments is insufficient to be detectable in vivo. Similarly, Mason and co-workers[4] were unable to detect consistent differences in patients with myocardial infarcts 24 hours after the administration of I^{131}. However, those authors used perchlorate to block the uptake of thyroid iodine and thus prevented any biosynthesis of thyroxine. At the same time, the perchlorate block contributed to a proportional increase in the iodide content of the stomach which would further complicate the radioactive scan of the heart. Another point of difficulty is that Mason and co-workers attempted localization in infarcts which were more than 8 days old and which had an average age of 15 days. It is not yet known at what point in the life history of an infarct its uptake will be maximal.

The fact that there is an increased concentration of any of the substances in the infarcted area, which by definition is ischemic, is surprising. It is clear that in the dog there must be an exchange of solutes between the blood and the infarcted area. This exchange is evident from our results and those of Carr and associates who followed the entry of mercury-[illegible] labeled chlormerodrin (Neohydrin) into infarcts in dogs and found high relative concentrations as soon as $2^1/_2$ hours after administration. On the other hand, Gunton and associates[5] using a much larger label in terms of molecular size (I^{131} labeled oleic acid albumin solution) found no concentration of the isotope in the infarcted area from 6 to 8 hours after the administration of the substance, and in some animals the radioactivity was decreased or absent in the ischemic areas. This may have been due to a slower equilibration of the tracer between blood and tissue.

There are a number of incidental findings which merit some discussion. For example, the iodide space in normal cardiac muscle was found to be between 0.39 and 0.42 ml. per gram. This is greater than the chloride space in myocardium, which has been estimated by various authors to be about 0.20 ml. per gram (see Table IV in Reference 6). This difference would suggest that half of the iodide space is intracellular. Furthermore, the iodide space in normal and infarcted heart muscle (0.95 and 1.41 ml. per gram, respectively) after T_3 and T_4 exceeds that after the administration of iodide. This would indicate that deiodination of the organic compounds must have occurred within the tissue. It is interesting to note that there was no diminution of this activity in the infarcted muscle. Similar data indicate deiodinase activity in both normal and incised skeletal muscle. This is consistent with the finding of deiodinase activity in skeletal muscle by Lissitzky and associates[7] and Tata.[8] A general discussion on this point is contained in a recent review of iodine metabolism.[9]

The role of thyroid hormones or iodide in the progression of the morphologic or metabolic changes in infarcted heart muscle, or indeed in normal heart muscle, is as yet unknown. For localization studies thyroxine clearly shows advantages over the other two iodo compounds. Clinically, this will depend on using thyroxine of sufficiently high specific activity, such that the chemical quantities of substance injected will be insufficient to cause any pharmacologic effects on the heart.

Summary

Increased radioactivity has been previously detected over the precordial area of patients with myocardial infarcts after the administration of NaI^{131}. A series of experiments was carried out in dogs to analyze the mechanism of this phenomenon. Infarcts were produced by coronary artery ligation. Twenty-four hours after the administration of NaI^{131}, the iodide space of infarcted myocardium was 1.7 times greater than that of normal heart muscle. Under the same conditions the ratios of infarcted to normal tissue were 1.5 and 3.3 for radioactive triiodothyronine and thyroxine spaces, respectively. There was also indication that these two iodoamino acids were deiodinated by both normal and damaged myocardium. Similar results were obtained when normal pectoral skeletal muscle was compared to the damaged muscle at the site of the thoracotomy in

cussion. An incidental finding of this study is that the iodide "space" is twice that reported for chloride.

These results indicate that the increase in the precordial radioactivity over the infarcted myocardium in vivo is due only in small part to the direct entry of iodide into the myocardium. Maximal uptake should occur after the iodide has been incorporated into endogenous hormone, i.e., thyroxine, which shows the highest concentration differential between normal and damaged myocardium.

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Case report

Ventricular fibrillation, a late complication of direct-current countershock

*Edwin L. Rotkfeld, M.D.**
J. Richard Zucker, M.D.
Asa H. Crews, Jr., M.D.
Arthur Bernstein, M.D.
Newark, N. J.

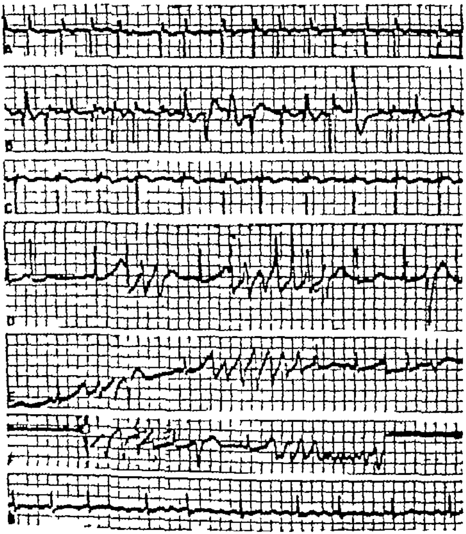
Since its introduction by Lown, synchronized direct-current countershock has become an increasingly popular therapy for various arrhythmias, both on an elective and emergency basis. Although the procedure would seem to be relatively safe, serious arrhythmias attributed to the shock have been reported. These have occurred in the immediate postshock period. The purpose of this report is to describe an instance of ventricular fibrillation that occurred more than 8 hours after the shock and to call attention to the fact that patients who have undergone direct-current countershock should be monitored for several hours after the procedure.

Case report

A 56-year-old woman had had atrial fibrillation of undetermined etiology for at least 10 years prior to attempted cardioversion. About 6 months before admission to the hospital she noted progressive dyspnea, orthopnea, weakness, and fatigue. She was digitalized with minimal improvement and given a maintenance dose of 100 mg. of digitalis leaf daily. An attempt to restore sinus rhythm with quinidine was unsuccessful. Physical examination showed a somewhat obese female in no acute distress. The blood pressure was 140/80 mm. Hg, the pulse rate was approximately 85 per minute, and the respirations were 20 per minute. Funduscopic examination showed minimal arteriosclerotic retinal vascular changes. The lung fields were clear to percussion and auscultation. There was atrial fibrillation with a ventricular rate of about 85 per minute. No murmurs or abnormal heart sounds were heard. The remainder of the examination was normal. The chest x-ray film was normal and an electrocardiogram showed only atrial fibrillation and digitalis effect. Complete blood count, urinalysis, blood urea nitrogen, protein-bound iodine, and serum sodium, chloride, and potassium were within normal limits.

On the day of the procedure she was given 100 mg. of digitalis leaf at 8:00 A.M. and 400 mg. of quinidine at 10:00 A.M. At 11:00 A.M. she was lightly anesthetized with intravenous sodium Pentothal. At that time a bipolar chest lead showed atrial fibrillation with a ventricular rate of about 110 per minute (Fig. 1 A). Ten minutes later she was shocked with 150 watt-seconds of direct current delivered just after the peak of the R wave. This was followed by atrial fibrillation and frequent multifocal ventricular premature systoles (Fig. 1 B). At 11:23 A.M. a shock of 150 watt-seconds was again given; this converted the arrhythmia to sinus rhythm (Fig. 1 C). Sinus rhythm was maintained and she returned to her room at 1:[illegible]0 P.M. under constant electrocardiographic monitoring. She had an uneventful afternoon and was given 400 mg. of quinidine at 4:00 P.M. At about 8:00 P.M. she suddenly had a grand mal seizure and the electrocardiogram showed paroxysmal ventricular tachycardia (Fig. 1 D). During the next hour she had at least [illegible] similar episodes associated with paroxysms of ventricular tachycardia and fibrillation (Fig. 1 E and F). After approximately 2,000 mg. of intravenous procaine amide

From the Hemodynamics Department, Newark Beth Israel Hospital, Newark, N. J.
Received for publication [illegible] 1964.
*Address: Newark Beth Israel Hospital, [illegible] Ave., Newark, N. J. [illegible]



F[illegible] 1 [illegible] from patient with atrial fibrillation. See text.

the ventricular arrhythmia ceased and atrial fibrillation was restored (Fig. 1C). Since then atrial fibrillation has persisted without further ventricular arrhythmias or clinical symptoms.

Discussion

In Lown's series cardioversion successfully terminated atrial fibrillation in 58 of 65 episodes.[1] In 35 of the 58 transient arrhythmias occurred in the immediate postconversion period. There were no late arrhythmias and no ventricular tachycardia or fibrillation. Killip described a case in which ventricular fibrillation occurred twice immediately after direct current countershock in the same patient. He warned that ventricular fibrillation was a potential complication of any form of shock therapy to the heart. Willis[4] recently reported an episode of ventricular fibrillation that occurred approximately 1 minute after the use of direct current in a patient with atrial fibrillation. He urged electrocardiographic monitoring for some time after direct-current countershock.

Our case is unique in that the ventricular arrhythmias occurred more than 8 hours after the shock. The reason for the delayed onset of ventricular fibrillation in this case is not apparent. Sensitivity to digitalis or quinidine seems unlikely since she had taken these drugs with impunity prior to the procedure. There was no clinical or chemical evidence of electrolyte imbalance. The Q-T interval of the supraventricular beat during the paroxysmal

ventricular arrhythmias was prolonged (Fig. 1 *D*) but the explanation of this is speculative

Lown stated in an early report that "No method of treatment should gain unquestioned acceptance until the late returns are in."[4] They are still coming in. This case demonstrates that ventricular fibrillation may be a late complication of direct current countershock. We believe that all patients should have constant electrocardiographic monitoring after this procedure.

Summary

A case of ventricular fibrillation that occurred 8 hours after direct current countershock for chronic atrial fibrillation is reported. A plea is made for constant electrocardiographic monitoring in the post conversion period.

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Clinical pathologic conference

*Hector Battifora, M.D.**
Marvin S. Rosenberg, M.D.
Maurice L. Bogdonoff, M.D.
Milton Weinberg, Jr., M.D.
Chicago, Ill.

Clinical abstract

History. The patient, a 23-year-old white man, was hospitalized because of severe dyspnea. The past history revealed that when he was 6 weeks old a diagnosis of congenital heart disease had been made. He grew up somewhat underweight and with a limited exercise tolerance. He could, however, engage in several athletic activities, such as tennis, skating, and touch football, with frequent rest periods. His condition remained quite stable throughout his childhood. Episodes of cyanosis of the lips associated with strenuous exercise occurred for a few years during childhood.

At the age of 18 he began to experience moderately severe exertional dyspnea. This led to his admission to another hospital, where a diagnosis of atrial septal defect was made. At operation no defect was found and only exploration was performed. Cardiac catheterization was performed prior to his discharge. His condition remained stable for about 4 years, except that during this time he was hospitalized elsewhere because of sharp chest pain, fever, expectoration, and dyspnea. He recovered and was discharged after 3 weeks.

When he was 22 years old the dyspnea became more severe, so that it was present even at rest. He was hospitalized again elsewhere and a cardiac catheterization was performed. The pulmonary arterial pressure was 74/24 mm. Hg, and the peripheral oxygen saturation was 86 per cent. A pulmonary arteriogram was obtained at that time. He was discharged on digitalis and diuretics.

Three months prior to his admission to Presbyterian-St. Luke's Hospital he noticed swelling of the ankles for the first time. His dyspnea had increased and he was anorectic. He was admitted to another hospital where he remained for 3 weeks with little improvement. A day after his discharge he felt sick and vomited several times. He was then admitted to Presbyterian-St. Luke's Hospital.

Physical examination. The patient was an asthenic Caucasian male who appeared to be weak but comfortable at rest. The oral temperature was 98 F., the pulse was 107 per minute, the blood pressure was 100/65 mm. Hg in the right arm, 95/60 in the left arm, and 125/80 in the left leg. There was no cyanosis, and the estimated venous pressure was 170 mm. of water. Examination of the lungs revealed no dullness, normal fremitus, and a moderate number of fine wet râles in the right base. The heart showed a point of maximal visible and palpable impulse in the fifth left intercostal space at the level of the anterior axillary line. Pulsations were present also over most of the precordium, being most forceful in the second and third left intercostal spaces and extending outward halfway to the left shoulder. P_2 was distinctly palpable, with a questionable thrill. S_1 and S_2 were loudest in the second and third left intercostal spaces. S_1 was single and pounding. S_2 was also pounding, with a wide fixed split. A diastolic gallop was audible over the left lateral border of the heart. No murmur or ejection click was heard. The abdomen was soft and there was no organomegaly. There was no sacral or pedal edema. The peripheral pulses were adequate.

Laboratory data. An electrocardiogram taken on admission revealed a ventricular rate of 115 per minute, with a P-R of 0.20 second, a QRS of 0.08 second, and a Q-T of 0.44 second. Sinus tachycardia with first-degree atrioventricular block, digitalis effect, and right ventricular hypertrophy was the interpretation. The hemoglobin was 16.7 Gm. per cent. The blood leukocyte count was 13,900 per cubic millimeter, being composed of 58 per cent neutrophils, 14 per cent band forms, 19 per cent lymphocytes, and 9 per cent monocytes. The urine had a specific gravity of 1.019, was clear, and had a pH of 5.0. It contained 1+ protein, 2 to 5 white blood cells per high power field, and rare red blood cells. Serum electrolytes were within normal limits.

Hospital course. Cardiac catheterization was performed on the day after his admission. The right heart chambers were entered via the saphenous vein. No evidence of right-to-left shunt was found

From the Divisions of Pathology, Medicine, Radiology, and Surgery, Presbyterian-St. Luke's Hospital, Chicago, Ill.
Received for publication Feb. 24, 1965.
*Address: Division of Pathology, Presbyterian-St. Luke's Hospital, 1753 West Congress Parkway, Chicago, Ill.

The main pulmonary artery was entered with difficulty and systemic pressures were encountered. The tip of the catheter could not be introduced into any of its branches. During the procedure the patient exhibited nausea, cough, and a syncopal episode that lasted 30 seconds. Shortly after returning to his room he became restless, slightly cyanotic, and developed a cardiac arrest from which he could not be resuscitated.

Discussion

DR. ROSENBERG This case concerns a 23-year-old white man in whom a diagnosis of congenital heart disease had been made when he was 6 weeks old. Congenital heart disease in infancy is often brought to the attention of the doctor by the mother because the child fails to thrive, has difficulty in breathing, or is cyanotic. It may be brought to the attention of the doctor because of these same signs, cardiomegaly, or, most commonly, a heart murmur. I will assume that the latter was the basis for the detection of this patient's heart disease. He was underweight and had a poor exercise tolerance, and I suspect that he was also underdeveloped. Cyanosis of the lips during strenuous exercise occurred for only a few years during his childhood, but no mention of generalized cyanosis or squatting was made.

When he was 16 years old his symptoms became more severe and he was operated upon for the repair of an atrial septal defect. However, none was found. Certainly one would not have expected an isolated atrial septal defect of the secundum type because of the detection of his heart disease at the age of 6 weeks. At this age there is persistence of the fetal pattern of the pulmonary vascular bed with an associated decrease in right ventricular compliance. Therefore, no significant left-to-right atrial shunt is manifested and the murmur (due to increased pulmonary flow) is not apparent. The murmur does appear later in infancy but usually is not detected until the child is 5 years of age or older, and even at this age its separation from an innocent pulmonary ejection murmur may be difficult. Subsequent to operation a cardiac catheterization was performed, but no data are provided in the protocol.

At the age of 21 he suffered an episode of sharp chest pain, fever, dyspnea, and expectoration; whether the latter was hemoptysis we are not told. This episode could have been pneumonia or perhaps pulmonary infarction. He then proceeded to develop increasing dyspnea to the point of its occurrence at rest. He underwent cardiac catheterization again, and now we are told of the presence of moderately severe pulmonary hypertension. The systolic pressure was 74 mm. Hg, presumably less than systemic. The diastolic pressure of 24 mm. Hg is quite low and suggests a diagnosis of pulmonary regurgitation or bilateral coarctation of the pulmonary arteries. In the latter condition there are congenital constrictions of the pulmonary arteries, usually at the origins of the right and left pulmonary arteries, with frequent poststenotic dilatation. More peripheral coarctations and hypoplastic segments are frequently present as well. There is usually a systolic pressure gradient across these constricted zones. It was pointed out by Agustsson and associates[1] that the diastolic pressure in the main pulmonary artery proximal to bilateral coarctations is quite characteristic in that the descending limb of the pulmonary arterial pressure is steeper than normal, the dicrotic notch is low and followed by a prominent dicrotic wave, and the end-diastolic pressure reaches a plateau and indeed approaches the end-diastolic pressure of the right ventricle. We are not told of the contour of this pulmonary arterial pressure.

Now the question is: What is the diastolic pressure in other diseases with pulmonary hypertension in the range of 74 mm. Hg? In my review of 50 patients with severe pulmonary hypertension due to mitral stenosis with pulmonary arterial pressure of 70 mm. Hg or greater, there was only one instance in which the diastolic pressure was below 30 mm. Hg. This was also true in cases of primary pulmonary hypertension and the Eisenmenger syndrome. The diastolic pressure of 24 mm. Hg suggests, therefore, bilateral coarctations of the pulmonary arteries. Arterial unsaturation of 86 per cent is also present. A pulmonary arteriogram was obtained, and I hope that we will have the opportunity of seeing it later.

During the last year of his life the patient required digitalis and diuretics for increasing dyspnea and systemic congestion.

admission to Presbyterian–St Luke's Hospital he was weak and vomited several times which suggests digitalis intoxication or splanchnic congestion On physical examination there was no cyanosis or clubbing yet erythrocytosis is suggested by the hemoglobin of 16 7 Gm per cent The point of maximum cardiac impulse in the fifth left intercostal space in the anterior axillary line suggests right ventricular enlargement but a lower left parasternal lift is not described His blood pressure was normal The blood pressure in the leg showed no evidence of coarctation of the aorta Venous pressure was not elevated Râles were heard in the lungs

A most remarkable physical finding was that of palpable precordial pulsations most forceful over the second and third left intercostal spaces and extending outward halfway to the left shoulder These findings are unique in my experience They suggest that one is palpating pulsations not only of the main pulmonary artery but also of the primary and perhaps even the secondary branches This finding has not been described in disorders in which the pulmonary arteries may be massively enlarged such as in high flow left to right shunts severe pulmonary hypertension or where poststenotic dilatation is present i e pulmonary valvular stenosis or coarctation of the pulmonary arteries It is conceivable however that in *the latter condition particularly if* proximal and distal obstructions are present one might be able to palpate these vessels The first heart sound is single and pounding being heard best at the second and third left intercostal spaces When one hears splitting of the first sound at the upper left sternal border one must suspect the presence of an S_1 pulmonary ejection click split Although S_1 is single in our case I suspect that it is a pulmonary ejection click which is in keeping with the large palpable pulmonary arteries S_2 was widely split with a palpable and markedly accentuated P_2 Certainly we find wide splitting of S_2 in atrial septal defect However the clinical picture does not suggest this diagnosis and we are told that none was present at operation Other conditions associated with wide splitting are right bundle branch block with which we do not have to concern ourselves here and pulmonary valvular stenosis wherein P_2 may be accentuated if the stenosis is mild but is normal or diminished with increasing degrees of obstruction In some cases of chronic pulmonary thrombosis multiple pulmonary emboli or bilateral coarctation of the pulmonary arteries one may find a widening of the A_2P_2 split with accentuation of P_2 due to delay in right ventricular ejection

A distressing feature of course is that no murmur was heard This makes it rather difficult to diagnose congenital heart disease However we do find this frequently in newborn babies and infants but only rarely in adults In the latter age group the absence of a murmur is most common in the Eisenmenger syndrome In cases of primary pulmonary hypertension one may not hear murmurs and in transposition of the great vessels a murmur may be absent or insignificant There is also the condition of cor triatriatum in which a diaphragm in the left atrium may produce severe obstruction with resultant severe pulmonary hypertension In these cases the pulmonary wedge pressure is elevated and the chest x ray film shows evidence of pulmonary venous obstruction The conditions mentioned above however are frequently associated with a nonspecific Grade 2 mid systolic ejection murmur *Since congenital heart disease was probably* diagnosed in this patient because of a murmur present in infancy the murmur either disappeared in adulthood or became so soft that it was undetected or perhaps it became located in an unusual position such as in the periphery of the chest and was not listened for The typical murmur in bilateral coarctation of the pulmonary arteries is a systolic ejection murmur that is heard best at the base with wide transmission toward the axillae and the back On occasion a continuous *murmur* may be heard when the obstruction is severe

The laboratory data are helpful in that the electrocardiogram showed sinus tachycardia first-degree A V block right ventricular hypertrophy and digitalis effect The Q T interval is quite prolonged and is bothersome since digitalis produces shortening of the Q T interval Perhaps

the Q-U interval was measured instead of the Q-T, in which case we might suspect hypopotassemia. However, the electrolytes on admission were normal.

On the day after admission the patient underwent his third cardiac catheterization, and no intracardiac shunt was present. Therefore, I attribute any unsaturation to intrapulmonary shunting, which may occur in any of the diagnoses under consideration. The main pulmonary artery was entered with difficulty and none of the branches could be entered. This suggests the presence of unusual anatomy or obstruction due to severe narrowing of the pulmonary artery, clots, or perhaps tumor (there have been cases of myxosarcomas of the main pulmonary artery). This might also be explained by bilateral coarctation of the pulmonary arteries or massive pulmonary thrombosis. The pulmonary arterial pressure was at systemic levels, and we can surmise that this pressure had increased since the first study 5 years before. During cardiac catheterization the patient experienced nausea, cough, and syncope. Shortly thereafter, cyanosis appeared and he died due to a cardiac arrest.

I believe that one diagnosis which I can make is that of severe thrombosis of the pulmonary arteries, probably at the secondary and tertiary branches since the vessels proximal to these were palpable. This probably began at age 21 with the episode of chest discomfort, expectoration, and fever, which I think was due to a pulmonary embolus with infarction or pulmonary thrombosis in situ. The development of additional thromboses and more complete pulmonary vascular occlusion, perhaps at the time of cardiac catheterization, was the probable cause of death. The syndrome of chronic thrombotic occlusion of the pulmonary arteries is receiving more attention since it is now correctable with the use of cardiopulmonary bypass. The etiology is usually multiple recurrent emboli from a peripheral source, of which we have no evidence in this patient, or thrombosis in situ. In the latter case this usually occurs in the presence of congenital heart defects.

Then what is this young man's primary defect? Primary pulmonary hypertension must be considered. This disease occurs most often in women in their twenties and thirties (rarely in childhood) and usually has a slow downhill course of 2 or 3 years. Minimal murmurs, if any, are present. Evidence of severe pulmonary and right ventricular hypertension is found by palpation, electrocardiogram, and x-ray film. This is a disease which can be strongly suspected at the bedside but is a diagnosis of exclusion at cardiac catheterization. The Eisenmenger syndrome can usually be excluded (which I think has been done in our case) by catheterization with the use of indicator dilution studies and angiocardiography. One must bend over backward to exclude correctable lesions, such as cor triatriatum or pulmonary venous obstruction due to anomalous connections of the pulmonary veins (a condition usually found only in infants). A case in point is discussed by Kjellberg and associates,[3] who in their textbook on congenital heart disease reported on a patient who had primary pulmonary hypertension but in whom a subsequent pulmonary arteriogram demonstrated bilateral coarctation of the pulmonary arteries. When all of the above-mentioned conditions are ruled out, one is left with primary pulmonary hypertension. The long history of cardiac disability and the presence of a congenital heart defect in infancy tend to exclude this diagnosis in this patient.

The most likely diagnosis is bilateral coarctation of the pulmonary arteries. This is based on the long history of congenital heart disease, the palpatory evidence of enlarged pulmonary artery branches, and main pulmonary artery systolic hypertension associated with a low diastolic pressure. The absence of the characteristic murmur can best be explained by its softness and probable peripheral location because of nearly complete obstruction of the pulmonary vessels due to severe coarctation and thrombosis, plus a low cardiac output which may render it inaudible. These cases are receiving more attention now because of the increased utilization of diagnostic procedures in patients with suspected congenital heart disease. In addition, the presence of this lesion in cases of supravalvular aortic stenosis, elfin facies, and



Fig 1 Chest film (see text)

mental retardation is receiving much current discussion If this is the correct diagnosis it is to my knowledge the oldest patient with isolated bilateral coarctation of the pulmonary arteries reported in the literature I look forward to the findings of Dr Bogdonoff and Dr Battifora

DR BOGDONOFF The chest films demonstrate many abnormalities In the plain film (Fig 1) taken shortly after his admission to this hospital the aorta is either normal or smaller than average The pulmonary artery on the left is difficult to identify Normally there is a density measuring 2 to 2 5 cm above the left bronchus and that is not present on this film There are several smaller densities which coalesce in this area On the right side there is a density in the place of the pulmonary artery which comes down and divides into tiny branches Also there is increased density throughout the medial portion of the right lower lobe I should like to direct your attention to the sparsity of pulmonary vascular densities throughout the mid zones and periphery of both lungs

In summary there is evidence of a sparse lesser circulation abnormal density in the parenchyma of the right lower lobe cardiomegaly and no abnormal or ectopic vessels in or about the great vessels The distal pulmonary arteries particularly in the right lower lobe are wider than one would expect in this peripheral portion of the lung Many of these findings can be clarified by reference to selected frames from an angiogram recorded elsewhere in 1962 (Fig 2) You can see that the main pulmonary artery shows no evidence of valvular or infundibular stenosis The artery proceeds toward the right lung and narrows Then it widens again and distally gives rise to a scimitar shaped vessel in the right lower lobe which widens as it proceeds distally This demonstrates the typical findings of multiple coarctations Let me direct your attention to the right upper lobe in which you can see only two branches and then an enormous air space with no vessels extending into it The findings here indicate probable occlusion with smaller vessels extending about the edge of the occluded segment The frames of the pulmonary angiogram that we have do not demonstrate the late circulation and it is often difficult to see the smaller vessels on pulmonary angiograms There is of course occlusion of the pulmonary artery on the left No contrast medium is seen extending into the distal branches in the frames that we have from the 1962 study

DR MCENSTER Can you distinguish between occlusion and absence of the pulmonary artery?

DR BOGDONOFF I do not know I cannot exclude congenital hypoplasia of the pulmonary artery to the right upper lobe On the left there is nonfilling of the lesser circulation I do not know whether it is due to thrombosis or to a congenital stenosis The angiograms that we have simply do not demonstrate this On the right side there are evidences of coarctation post stenotic dilatation and abnormal widening of the vessels suggestive of stenosis of smaller branches in the right lower lobe because the vessels distally are so large extending down to the diaphragm In congenital absence of the pulmonary artery there is usually dislocation of the heart toward the involved side due to hypoplasia of the lung Moreover when the congenital absence is on the left side there are usually associated cardiac anomalies



Fig 2 Selected frame from an angiogram recorded in 1962 (see text)

This patient does not show any of the stigmata of congenital absence of the pulmonary artery. I think that the findings here are consistent with embolus to the stenosed main pulmonary artery on the left side with no recanalization. The findings on the right are somewhat difficult to explain. I have never seen a pulmonary angiogram showing poststenotic dilatation after recanalized embolic stenosis. I would consider therefore that the findings are those of congenital coarctations with poststenotic dilatation on a hemodynamic basis.

DR BATTIFORA Dr Rosenberg and Dr Bogdonoff have arrived at a correct diagnosis. I shall now show you the findings at necropsy. There were hypertrophy and dilatation of the right atrium and right ventricle but no congenital defects of the heart. No thrombi were found in the cardiac chambers or peripheral venous system. There was marked hepatic and splenic congestion and no other findings of importance in organs other than the lungs. The pulmonary valve was of normal diameter and its leaflets were normal. The main pulmonary artery was dilated. Its wall was thick and there were numerous atheromatous plaques in the intima. Shortly beyond its origin the left pulmonary artery became markedly narrowed retaining only a questionable filiform lumen (Fig 3). Beyond the region of stenosis which measured 4 cm in length the left pulmonary artery and its branches were hypoplastic. The right pulmonary artery on the other hand showed extreme dilatation and severe atherosclerotic changes. Several regions of moderate stenosis and poststenotic dilatation were present in this vessel. The branches which supplied the right upper and middle lobes showed points of stenosis with several instances of almost complete atresia.

The trachea and bronchi were normal. The left lung was markedly decreased in size. The lobes of the left lung and the middle and upper lobes of the right lung were normal in color and consistency. The right lower lobe was indurated, dark brown in color and contained several areas of hemorrhagic infarction. Microscopic studies of the left lung showed a few collections of hemosiderin laden macrophages within alveoli. The alveolar walls were of normal thickness. The arteries and arterioles in this lung were not hypertrophic. Occasional areas of focal fibrosis consistent with old pulmonary infarction

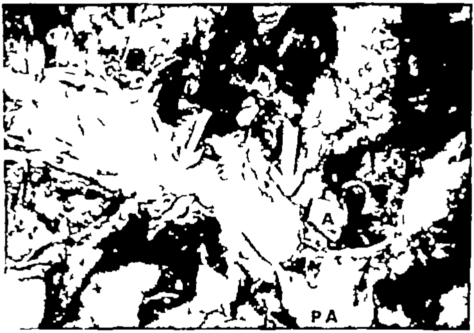


Fig 3 View f the opened pulmonary arterial tree The markedly stenotic left pulmonary artery is indicated by the black rrow Beyond the area of stenosis there i moderate hypopla ia of the vessel The right pulmonary artery kedly dilated with several areas of mild stenosis (*white arrows*) The intima has a goose flsh ppearan e due tc the presence of numeron tiny atheromatous plaques The right lower lobe appears dark l l rated *PA* Main pulmonary artery A Aorta

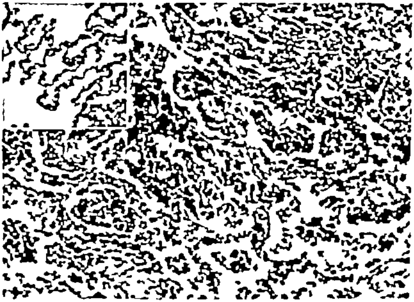


Fig 4 Section of the right lower l be The al eolar capillaries are packed with red blood cell There i some fibrosis of alveolar wall The air paces re filled w th hemosiderin-conta nin macrophages The inset sho a comparable area in the left upper lobe in which the alveolar capillaries are th n ar l bloodless

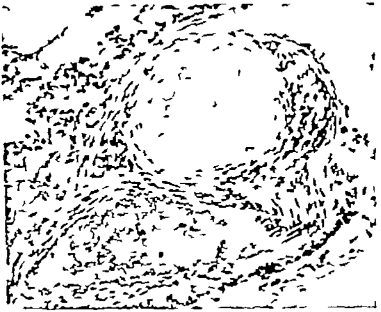


Fig. 5. Microscopic section showing organizing thrombus in a small branch of the right pulmonary artery.

were seen particularly in the upper lobe. The sections taken from the right lower lobe showed severe congestion of alveolar capillaries which contrasted with the relatively bloodless alveolar capillaries in the remainder of the lung. There were also fibrosis of alveolar walls and extensive intra-alveolar collections of "heart failure cells" (Fig. 4). The arteries and arterioles displayed marked hypertrophy of their muscular walls, and several of them contained old or recent thrombi (Fig. 5). The parenchymatous and vascular changes in this lobe were those of chronic pulmonary hypertension. These changes were absent in the rest of the lung, which apparently was protected from the hypertensive effect by the stenoses in the arteries supplying it. Sections taken from the pulmonary trunk showed a markedly thickened and fibrotic intima. These changes were accentuated in the sections taken from points of stenosis in the different branches of the arterial tree. The left pulmonary artery (Fig. 6) displaying the greatest stenosis contained a large intimal plaque composed of collagen, elastic tissue, small blood vessels, and a myxomatous stroma. The media beneath showed that this had an accentuated acidophilic staining of its elastic tissue. In the areas of poststenotic dilatation, intimal plaques of varying thickness were seen. The media in these regions was narrowed but otherwise normal.

In summary, the postmortem findings showed virtually complete stenosis of the left pulmonary artery, severe stenosis of the branches supplying the right middle and upper lobes, and mild stenosis of the branch to the right lower lobe. These were apparently caused by a congenital developmental defect. There were multiple poststenotic dilatations in the involved vessels. Multiple old and recent thrombi were found within the lesser branches of the pulmonary arterial tree supplying the right lower lobe. Old and recent infarcts were associated with these. Arterial and parenchymal changes consistent with long-sustained pulmonary hypertension were present in the right lower lobe but absent elsewhere. The right cardiac chambers were hypertrophied and dilated.

DR. BOGDONOFF: Were there venous thromboses?

DR. BATTIFORA: It is difficult to differentiate microscopically small pulmonary veins from peripheral branches of the pulmonary arterial tree. Some of the thrombi were probably within small veins, but the majority were within arteries which, when relatively large, are easily identifiable.

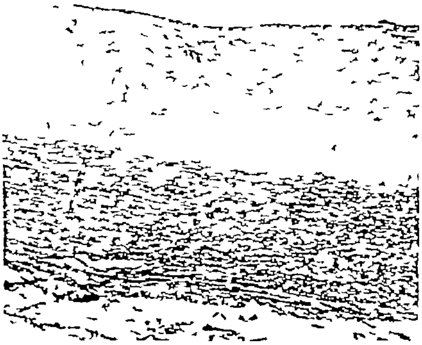


Fig. 4. Section taken through the stenosed left pulmonary artery showing marked intimal thickening due to deposition of collagen and amorphous matrix and a few cholesterol clefts.

their internal elastic membranes. Pulmonary venous thrombosis as a complication of peripheral pulmonary arterial stenosis or thrombosis is quite frequent and is to be expected, especially when there is infarction of the lung or myocardial insufficiency with pulmonary edema and congestion.

QUESTION FROM AUDIENCE: Could some of the areas of stenosis be due to thrombosis with subsequent recanalization?

DR. BATTIFORA: That is a likely possibility. In the late stages of organization of a thrombus it is often impossible to distinguish it from a fibrous atherosclerotic plaque. The process of repeated thrombosis has, I believe, played a major role in the worsening of this patient's symptoms. It is regrettable that no pulmonary arteriograms were obtained earlier in the patient's life, since they would have undoubtedly provided information about the progression of this disease.

DR. ROSENBERG: Perhaps Dr. Weinberg can tell us something about the surgical treatment of this disorder.

DR. WEINBERG: This case is a remarkable example of obstruction to pulmonary blood flow at multiple levels—in the left main pulmonary artery, in the secondary, tertiary, and distal arterial branches of the right upper and middle lobes, and at the arteriolar level of the right lower lobe. Congestion and disruption of pulmonary parenchyma by the infarct of the right lower lobe provided the final increments of obstruction and hypoxia.

Surgical correction of pulmonary artery stenoses is feasible in the localized lesions of the common trunk and of the right and left main branches. These most often occur as narrow coarcted segments followed by poststenotic dilatation. The procedures which have been applied to relieve these obstructions include resection and end-to-end anastomosis, bypass graft, linear incision and enlargement with a patch, or even a diversion of blood flow with a superior vena cava-to-right main pulmonary artery shunt. Stenoses of the secondary branches have been successfully relieved in a few reported cases, but they are usually associated with additional distal lesions of vessels too small for surgical repair. Diffuse hypoplasia of the pulmonary artery and its branches is an additional variation of this group of lesions for which there is no satisfactory treatment.

The stenoses of the pulmonary artery

branches in the right upper and middle lobes in this patient involved vessels too distal and small for consideration of surgical relief Stenosis of the left main pulmonary artery however may well have been suitable for surgical correction at one time This would have depended upon whether the hypoplasia distal to the stenosis was a primary defect precluding satisfactory flow through the lung or was the result of diminishing flow as the stenosis of the left main branch progressed to occlusion

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Hypertrophic obstructive cardiomyopathy

Norman Krasnow, M.D.
Brooklyn, N. Y.

Since the first clear demonstration by Brock[1] in 1957 that the left ventricular myocardium could hypertrophy in such a manner as to obstruct its own outflow tract, a burgeoning literature attests to the practical and theoretical interest in this peculiar condition. In recent years a variety of pathologic entities causing obstruction to left ventricular outflow has been recognized by the increased use and accuracy of left heart catheterization and selective angiography. Classified broadly into two groups, obstruction to left ventricular outflow may be caused either by a narrowed, fixed orifice or by a dynamic obstruction existing only during systole and susceptible to spontaneous or deliberate fluctuations in severity. The fixed obstructions include valvular stenosis, either congenital or acquired;[2] subaortic stenosis of the discrete or fibrous diaphragmatic type; and supravalvular stenosis, sometimes associated with mental retardation. The left ventricular myocardium, although hypertrophied, has not been considered to be inherently abnormal in this group. The dynamic form of obstruction, here referred to by Goodwin's broad designation "hypertrophic obstructive cardiomyopathy," has also been known as muscular,[7,8] functional,[9,10] or idiopathic[11] hypertrophic subaortic stenosis, asymmetrical hypertrophy,[12] and hereditary cardiovascular dysplasia.[13] Although the characteristics of the syndrome are now well defined, its existence as one or more nosologic entities is still unclear and is the subject of continuing descriptive reporting. The extensive experience at one center has recently been exhaustively reviewed.[14]

As in the case of other newly recognized diseases, early reports were pessimistic about the possibilities for clinical or antemortem diagnosis or corrective therapy. In half a decade these forebodings have given way to justified optimism in clinical and laboratory diagnosis and to cautious experimentation in surgical treatment.

Clinical features

Obstructive cardiomyopathy presents to the clinician in a variety of ways. The patient may be asymptomatic and examination is performed at the request of the private physician for evaluation of a murmur or cardiac enlargement. On detailed questioning, the patient may report only mild breathlessness or fatigue on exertion. Many cases have been discovered as part of a family survey after a similar diagnosis has been made in a relative, or after a sudden death prompts family inquiry. On the other hand, when examination is

From the Department of Medicine, State University of New York Downstate Medical Center, and Medical Service, Kings County Hospital Center, Brooklyn, N. Y.
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Address: Department of Medicine, State University of New York Downstate Medical Center, 450 Clarkson Ave., Brooklyn, N. Y. 11203.

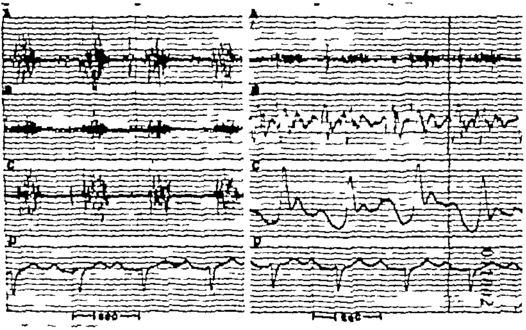


Fig 1 *Left* Phonocardiogram (frequency range A 0-140 c.p.s B 140-250 c.p.s C 50-500 c.p.s.) shows an atrial gallop and diamond-shaped systolic murmur *Right* Phonocardiogram with carotid pulse The carotid pulse (*C*) shows the rapid upstroke to early peak and rapid fall to small secondary systolic wave The systolic murmur is loudest *after* the peak pressure is reached There was a gradient of 100 mm Hg at rest

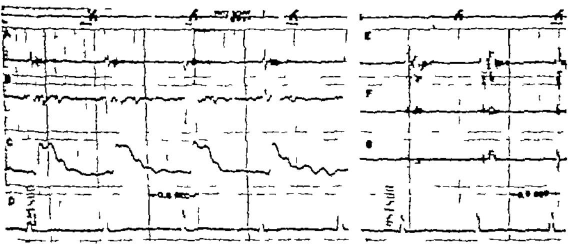


Fig 2 The carotid pulse (*C*) shows a mid-systolic secondary wave and late onset of systolic murmur (*E F G*) An ejection sound is not seen The aortic second sound is preserved This patient had no gradient in the outflow tract at rest but a systolic mean gradient of 30 mm Hg after isoproterenol (3 μg per minute)

prompted by signs or symptoms they often resemble those of aortic stenosis but with atypical features: the murmur is not at the base, there is no murmur or thrill in the neck, the pulses are unusually brisk, there is a small aortic knob on x-ray examination usually without poststenotic dilatation, there is no calcification of the aortic valve. Congestive heart failure and cardiac enlargement may not be associated with prior history of heart disease or rheumatic involvement, save perhaps for a mild "functional" murmur (a truly accurate term in this instance, as will be seen).

As in valvular aortic stenosis, the major symptoms are dyspnea on effort, angina pectoris, fatigue, syncope.[7,11,13] Palpitations are noted in a small percentage of cases. These symptoms usually have their onset in young adult life, but occasionally may first appear in the fifth or sixth decade. Cases have been reported in infants.[16,18] The disease is several times more common in men than in women.[7,11,13] The angina of effort may transiently increase in severity immediately *after* exercise, correlating with a temporary increase in the pressure gradient.[4,6] Contrary to the inexorably fatal course when symptoms develop in valvular aortic stenosis, the symptoms in obstructive cardiomyopathy may persist and sometimes remain unchanged for years,[1,7] up to 18 years in one case. However, sudden death is common.

The physical findings originally detailed by Braunwald and Gorlin[4] are frequently striking, especially by comparison with those in valvular aortic stenosis, and permit bedside diagnosis. Although both valvular and subvalvular stenosis have in common a loud systolic ejection type of murmur (Figs. 1 and 2), the classic pulsus parvus and tardus of the rigid, fixed obstructive lesions is replaced by a sharply rising, almost bounding pulse of bisferiens type (but not exactly—see below). The murmur is characteristically in the fourth or fifth intercostal space on the left, near the sternum, and tends to radiate to the axilla or the base, but unless very intense is not well heard in the neck. It tends to begin later in systole[7,9] after the onset of the aortic pressure curve (Fig. 2). Early systolic ejection clicks are not common but may occur.[11,18,7] The aortic component of the second sound is well preserved. Other findings, such as palpable double apical impulse, paradoxically split second sound, gallop rhythm, and pansystolic murmur of mitral insufficiency, are not infrequent, although they are not distinguishing features from valvular aortic stenosis. Early blowing systolic murmurs have been noted by some authors[13,14,1] but are very rare. (The subvalvular "cone" area seen on selective angiography to persist in diastole would be a potential source of such murmurs.) Occasionally, the hypertrophied septum acts also as an obstruction to inflow, producing a rumbling mid-diastolic murmur at the apex.[4,13] When septal enlargement also impedes right ventricular outflow, a parasternal lift or heave suggestive of right ventricular hypertrophy may be noted and large a waves are seen in the jugular pulse.

These physical findings may be confirmed by graphic recording of apex and carotid pulses. The apex pulse shows a large a wave and a sharp mid-systolic or late systolic outward thrust.[18,19] The carotid pulse tracing has become a characteristic feature of the disease. Hartman[11] and Soulié and associates[3] noted its unusual form in early reports, and the heuristic report of Braunwald and Gorlin[4] brought its significance into prominence. Contrary to the situation in severe valvular aortic stenosis in which the pulse rises slowly with an anacrotic notch, a shoulder at the peak, and slurred downstroke with a poorly defined dicrotic notch, the upstroke of the carotid pulse in hypertrophic obstructive cardiomyopathy is more rapid than normal and has no anacrotic notch. It peaks early in a sharp spike, declines rapidly to a plateau or upward convexity in the latter part of systole (giving the sensation of bisferiens pulse to the palpating fingers), and ends in a sharply defined dicrotic notch (Figs. 1 and 2). Braunwald[17] used an electronic differentiating circuit to quantify the increased rate of rise in pressure and noted some overlap with normal values, as did Wigle,[13] but clear separation from valvular aortic stenosis. However, these authors and Bottcau and Alkenstein[14] noted a short absolute time to peak pressure. The original hypothesis[11]

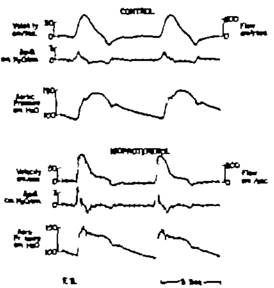


Fig. 3 Simultaneous aortic velocity and pressure recording during the control state and after isoproterenol in a subject with hypertrophic obstructive cardiomyopathy. The control curves are normal. After isoproterenol the peak ejection velocity is increased and the pressure contour is changed (cf. Figs. 1 *right* and 2). The major portion of outflow is completed in the first half of systole. (From Hernandez et al.: *Journal of Clinical Investigation* 43: 401, 1964, by permission.)

that the sharp percussion wave represented ejection which was then impeded by progressively severe functional obstruction has been confirmed by actual measurement of blood velocity[36] (Fig. 3). Peak blood velocity and flow in 5 cases did not differ markedly from control values; however, the control subjects ejected 57 per cent of the stroke volume in the first half of systole, whereas patients with hypertrophic obstructive cardiomyopathy ejected 70 to 85 per cent. Pierce, Morrow and Braunwald[34] noted similar findings in patients during open thoracotomy. The additional contraction in later systole against the obstructing septum is presumably the cause of the characteristic secondary double mid-systolic thrust in the apex cardiogram. The tidal wave in the arterial pulse is not a secondary rapid ejection but is considered to represent a rapid deceleration phenomenon or perhaps a reflected wave.[36] The cause of the anacrotic notch on the left ventricular pulse is not precisely understood (Figs. 4 and 5).

The electrocardiogram is usually abnormal.[illegible] The changes most commonly include those associated with valvular aortic stenosis, namely, left ventricular hypertrophy with strain pattern and varying degrees of left bundle branch block. The ST-T changes may be out of proportion to the pressure gradient.[illegible] In addition, left axis deviation is often noted. P wave abnormalities are common, including a large broad P wave especially in Leads II, III, aVF and a deep negative component of the P wave in Lead V1. Estes interpreted these changes as reflecting left atrial enlargement and intra-atrial block. Disturbances in cardiac rhythm occur—bouts of atrial fibrillation and ventricular extrasystoles—but are not the usual state of affairs. Large Q waves may be observed or poor progression of the R wave in the precordial leads suggesting myocardial infarction in occasional cases but actually reflecting the septal hypertrophy.[illegible] The Wolff-Parkinson-White syndrome has been observed by several authors.[illegible] Vectorcardiographic tracings[illegible] are frequently abnormal, also suggesting myocardial infarction, left ventricular hypertrophy and conduction defects. Early posterior orientation of electrical forces is commonly noted as well as consistent posterior orientation of the late vectors.

The radiographic appearance of the heart is not characteristic. The left ventricle is prominent, suggestive of concentric hypertrophy, although the cardiothoracic ratio may be normal.[illegible] The pressure gradient does not correlate with cardiac size.[illegible] The presence of calcification of the aortic valve or poststenotic dilatation of the ascending aorta strongly indicate that, with rare exceptions,[illegible] obstructive cardiomyopathy is not present (or at least that it is not the sole lesion). Right ventricular enlargement may also be observed. Left atrial enlargement is common.

Cardiac catheterization

Once suspected, the diagnosis of hypertrophic obstructive cardiomyopathy may be confirmed by appropriate cardiac catheterization and selective angiography. Establishment of the existence of a systolic



Fig. 4. Simultaneous left ventricular–brachial arterial pressures and direct pullback across the outflow tract. Note the notched upstroke on the left ventricular pulse and the spike and plateau contour in the subvalvular chamber and ascending aorta.

pressure gradient between the left ventricle and peripheral artery does not define the lesion precisely, since this of course is present with valvular or discrete subvalvular or supravalvular stenosis as well. Thus transseptal or percutaneous techniques of entry into the left ventricle may be diagnostically inadequate, whereas a direct pullback tracing from the left ventricle to the aorta will demonstrate the typical subvalvular aortic valve itself (Fig. 4). The left ventricular pulse characteristically shows a notch on the upstroke at or slightly above the peak level of arterial pressure. The gradient may be missed if the catheter is not advanced deep into the left ventricle, or the chamber may be missed if the pullback tracing is contaminated by many extrasystoles. However, the notched left ventricular upstroke, the typical arterial contour, and the response to physiologic maneuvers (see below) may strongly suggest muscular obstruction even if a chamber is not recorded.

Cardiac output is usually well maintained or may be above normal until late in the course of the illness.[14] Left atrial and left ventricular end-diastolic pressures are often elevated, but in view of the severe hypertrophy and small ventricular cavity, it is likely that this represents altered left ventricular distensibility rather than ordinary congestive heart failure.

The dynamic character of the muscular stenosis has been demonstrated in several ways. Whalen,[19] Braunwald,[8,9] and Krasnow[14] and their respective associates have noted that certain patients may have no demonstrable gradient at rest; this may even be noted in the same patient at various times, especially at the time of surgical exploration. However, when the heart is stimulated by isoproterenol, digitalis, or exercise, a gradient may be developed which clarifies the diagnosis. The Valsalva maneuver[8,14] and the inhalation of amyl nitrite[17] or sublingual nitroglycerin[14] have also been shown to produce or increase a gradient in these patients.

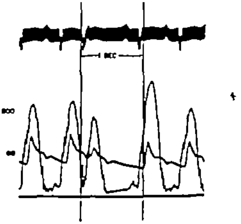


Fig. 5. Simultaneous left ventricular–brachial arterial pressures during a[illegible] premature contraction. The beat which follows the premature [illegible] shows an increased left ventricular pressure with decrease in arterial pressure and pulse pressure.

A useful sign is the dissociation of pressures which follows an extrasystole (Fig 5). Brockenbrough, Braunwald and Morrow[15] noted that the long diastolic pause after an extrasystole produces an increase in left ventricular pressure as expected, but the simultaneous arterial pressure and pulse pressure are decreased or unchanged. In normal subjects or in patients with discrete aortic stenosis the arterial and ventricular pressures rise concordantly and the pulse pressure increases. Presumably in obstructive cardiomyopathy the more forceful postextrasystolic con

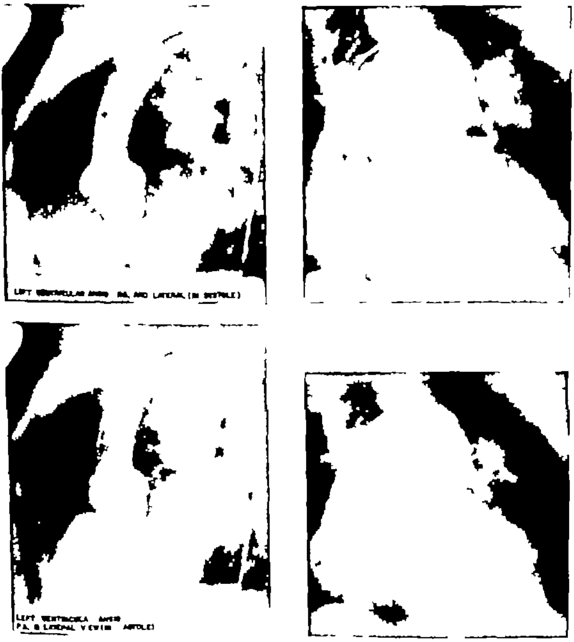


Fig 6 Selectiv left entricul ngiogram The ventricular ca ty is distorted by the hypertroph c septum encroaching from th right and ferorly predom nantly during systole Note the subvalv lar cone area in systole nd diastole The anter or wall is also thick The scend ng aorta is not dilated

traction induces a similar increase in the force of contraction of the obstructive hypertrophied muscle as well decreasing still further the effective orifice area. Other investigators have consistently confirmed the usefulness of this sign.[7,14] When this sign is absent in patients with hypertrophic cardiomyopathy the obstruction may not be severe at that time.[14]

Selective angiography demonstrates marked thickness of the ventricular wall with a small distorted ventricular cavity (Fig. 6).[7,11,...] This distortion is produced in part by the thick muscular septum encroaching on the posterior inferior aspect of the left ventricular chamber. The aortic valve and sinuses of Valsalva are normal, but below there is an inverted cone-shaped area ending in a constriction 3 to 5 cm. below the aortic valve. This cone may persist in diastole, although the area of greater constriction may be decreased. Some patients have equally distorted ventricular cavities without demonstrable obstruction to outflow.[..]

Pathology

Whereas most diseases are recognized initially in the postmortem examination and then related to clinical syndromes, the reverse has been true of hypertrophic obstructive cardiomyopathy. Only when the surgeon could open the living and especially the beating heart expecting to find a valvular stenosis was the obstructive character of the septal hypertrophy clarified and the full significance of older reports of concentric or eccentric hypertrophy appreciated.[..] Even after clinical recognition the surgeon or postmortem dissector may be deceived by an arrested heart.

The dominant feature at pathologic examination[...] consists of massive hypertrophy of the interventricular septum sometimes measuring 2 to 3 cm. in thickness. There is often accompanying hypertrophy of the free wall of the left ventricle and the papillary muscles as well, but the ratio of thickness of septum to anterior wall is still increased.[14] Some reports emphasize the obstruction is a ridge of muscular and superimposed fibrous tissue running from septum to anterior free wall. The endocardium is thickened and fibrous, and focal areas of myocardial fibrosis assume varying degrees of prominence. The left ventricular cavity is decreased, sometimes markedly so. Microscopic examination demonstrates hypertrophied muscle fibers, usually with bizarre patterns of fiber arrangement and sometimes with vacuolization, loss of striation, and separation of fibers by connective tissue. In some specimens light microscopy reveals no abnormality. Definitive evidence of prior inflammatory disease has not been adduced. Pearse[14] found thick but short fibers with an increase in nerve fibrils and capillaries, histochemical evidence of an increase in glycogen, phosphorylase and monoamine oxidase, and electron microscopic resemblances to sinoauricular nodal or atrial tissue suggesting anomalous development of atrial or autonomic nervous tissue. Braudo, Wigle, and Keith[..] have noted differences in the microscopic pathology of the abnormal septum and the "normal" free wall of the left ventricle. Two reports of familial cardiomyopathy without proved obstruction showed histochemical evidence of polysaccharide deposition.[..]

Etiology and pathogenesis

A variety of causes of obstruction of the outflow tract has accumulated in addition to the previously listed lesions. This group is unrelated to septal hypertrophy or idiopathic cardiomyopathy and includes massive infiltration of the heart with glycogen[..] or rhabdomyoma[..] or abnormalities of the mitral valve. The anterior leaflet of the mitral valve may be abnormally placed[...] or the site of accessory tissue[..] or may be distorted in position after repair of an A-V communis defect.[..] We have observed 2 cases in which mild obstruction of the right ventricular outflow tract was caused by an aneurysm of the sinus of Valsalva.[..] Common causes of left ventricular hypertrophy such as hypertension, valvular aortic stenosis, or coarctation may promote a secondary subaortic muscular stenosis.[...] This secondary hypertrophy was considered in the thinking of the earlier writers to be a probable common etiology of obstruction to outflow, although most subsequent reports, including Brock's,[..] have empha-

sized the primary character of the cardiomyopathy.

Obstructive cardiomyopathy has only rarely been associated with other forms of heart disease. The not uncommon association of subaortic and subpulmonary stenosis[7,16,31,39] may represent a greater degree of the same primary process with bulging of the septum into the right ventricle. The disputed Bernheim syndrome[32,44] may fit this group. Lauer and associates[41] and Becu and associates[40] have reported patients, usually infants, with ventricular septal defect, some of whom had hypertrophic ridges on the rim of the defect causing obstruction to left ventricular outflow. Hypertrophic obstructive cardiomyopathy has also been reported[17] in association with Turner's syndrome and mitral and tricuspid insufficiency. Molthan, Paul and Lev[78] have reported the association of subaortic stenosis with complete A-V canal and valvular pulmonary stenosis. We[72] have studied one patient with hypertrophic obstructive cardiomyopathy who had severe subaortic and mild subpulmonary stenosis. In addition, there was a severe valvular pulmonary stenosis, an atrial septal defect, hemorrhagic pericarditis and multiple noncardiac congenital anomalies including pectus excavatum, reduplication of the renal pelvis, micrognathia, severe myopic degeneration of the retina and mental retardation.

The difficult question at present is whether the patients with subvalvular obstructive phenomena represent a distinct and separate disease entity *sui generis* or, more likely, constitute part of a spectrum of those cardiomyopathies without demonstrable obstruction of the outflow tract. Certainly, the recent demonstration of the dynamic character of the obstruction, with the need to stimulate certain hearts with drugs or physiologic maneuvers in order to bring out the obstructive component, suggests that some cases previously classified simply as idiopathic cardiomegaly may have been missed. Goodwin classified the cardiomyopathies into three types—restrictive, congestive and obstructive. Whereas the congestive and restrictive types commonly present with severe congestive failure, arrhythmias and mural thrombi with peripheral embolic phenomena, the obstructive type is less dominated by these clinical findings and more by the presence of an obstruction of the outflow tract with the related symptoms described above. Braunwald and Aygen[7] added a fourth category. They observed families with cardiomyopathy in several members, only some of whom had demonstrable gradients. The clinical picture was more that of the obstructive type of cardiomyopathy, rather than congestive or restrictive, but nevertheless, even the infusion of isoproterenol could not produce a gradient. Half of these patients had hypertrophy of the free wall of the left ventricle, not of the septum. Cohen and associates[19] have also described similar cases.

Clinical studies in man and experimental procedures in dogs have established that certain agents or physiologic procedures may alternately create or abolish pressure gradients across the outflow tract. Thus catecholamines (isoproterenol,[19,26,41,44] norepinephrine,[66,73] phenylephrine plus atropine[43]), calcium chloride,[14] postextrasystolic contractions,[4] ouabain,[74] exercise,[19,6] amyl nitrite,[47,73] nitroglycerin,[44] Valsalva maneuvers,[26,8] normal respiration,[14,66] hypothermia,[73] low cardiac output,[73] decreased circulating blood volume,[14] and hemorrhagic shock[74] have all been associated with significant pressure gradients. Conversely, gradients have been abolished by methoxamine,[43,77] aortic constriction,[38,73] blood transfusion[38,44] or general anesthesia. The original thesis[44] that some of these agents acted through an inotropic mechanism, altering the rate of fiber shortening, has been challenged[47] by the concept that reduction or expansion of left ventricular volume is the important parameter in increasing or decreasing the gradient. Thus, the changes in ventricular volume with the Valsalva maneuver or amyl nitrite or hypothermia are attributed to this mechanism. In 2 dogs studied in our laboratory[66] in which gradients were induced by norepinephrine or phenylephrine plus atropine, the mean rate of circumferential fiber shortening in the left ventricle did not change, whereas ventricular volume decreased markedly (Fig. 7). In 2 patients[23] the instantaneous aortic flow contour was not altered by

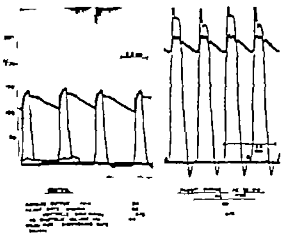


Fig. 7. Subaortic stenosis produced in the normal dog. Note the change in pulse contours. In this case despite the high systolic pressure the end-diastolic volume is markedly decreased. The mean fiber shortening rate is not significantly altered.

doses of methoxamine. On the other hand the presumption that the effect of digitalis or isoproterenol is due to their well known influence in decreasing ventricular volume may not be applicable to the specific cases cited since left ventricular end-diastolic pressure was frequently *increased* by these agents. In the absence of marked changes in distensibility, this would imply, at least directionally, a similar increase in volume. Lewis[77] decreased the gradients in 7 patients with methoxamine despite a decrease in measured ventricular volume in one. Hernandez and associates[23] suggested that the small ventricular volume may be *secondary* to an unusually forceful early systole. Braunwald and co-workers[14] suggest that various factors play conflicting roles in these physiologic responses. These include inotropic influences and effects on ventricular volume such as venous return, arterial pressure, and heart rate.

The fundamental etiology of obstructive cardiomyopathy is enigmatic. A congenital etiology is suggested by the occurrence in infants and neonates[11, 14, 49] and by the occasional association with other congenital defects[17, 69, 71] but, on the other hand, Muesham[71] reports instances of adults with idiopathic cardiomegaly who had documented normal-sized hearts several years before the disease was recognized. A familial pattern with autosomal dominant inheritance is reported in 20 to 30 per cent of the cases,[7, 8, 12, 13, 2] traceable in some cases for three or more generations.[13] Keith's[77] early hypothesis that subaortic stenosis represents failure or proper evolution of the primitive bulbus cordis has been attractive and would account for the frequent association with subpulmonary stenosis. However, the generalized hypertrophy of the ventricle is not thus explained unless one assumes that it is secondary to an earlier stage of more localized hypertrophic obstruction. Klein and co-workers[14] measured left ventricular end-diastolic volume in 6 cases. Compared with normal volume values of 96 ± 20 ml. per square meter or values of 148 ± 33 ml. per square meter in patients with aortic stenosis, the volumes in patients with hypertrophic obstructive cardiomyopathy were 71 ± 10 ml. per square meter, even though aortic valve gradients were small in several cases. These data would support the concept that a decrease in ventricular volume is primary, a function of a generalized cardiomyopathy rather than a secondary nonspecific response to hypertrophy. The decreased cavity-to-wall ratio and poor correlation of left ventricular hypertrophy with systolic pressure is consistent with this hypothesis.[71] A hypothetical analysis by Robb and Robb[77] of obstruction as a possible consequence of premature contraction of the normal deep bulbospiral muscle has not thus far been demonstrated experimentally. The absence in some cases of significant differences in the excitation pathways recorded electrocardiographically or vectorcardiographically does not support this hypothesis. On the other hand, Ovadjian and Randall[79] have recently shown that in normal dogs the mechanical contraction of the superficial muscle at the base of the heart may precede that of the apex by a few milliseconds unrelated to the sequence of electrical activation. These time differences were decreased by stellate ganglion stimulation resulting in greater synchrony of contraction. Transaortic pressure gradients were not measured. Harwood[14] showed that isoproterenol altered the sequence of contraction of the infundibulum of the right ventricle, producing minimum rather than maximum segment length of

the infundibulum at peak isovolumic tension. It has been postulated[22] that some of the reported improvements after surgical excision or incision of the hypertrophied system have been due to the production of left bundle branch block with slowing of the rate of left ventricular contraction.

Krasnow and co-workers[61] suggested that patients with hypertrophic obstructive cardiomyopathy may have an abnormal sensitivity to catecholamine stimulation and that their condition may represent a more severe form of the hyperkinetic heart syndrome.[61] The decrease in time to peak arterial pressure[27, 61] (although rate of rise in pressure and peak blood velocity and acceleration were not consistently increased per se)[27, 32] is similar to the normal response to inotropic stimulation. Pronethalol, a β-adrenergic blocking agent, had little or no effect on the obstruction in the resting state,[28] although it blocked the aggravation by isoproterenol and exercise in the latter state without affecting cardiac output.

Right ventricular obstruction

Less is known about subpulmonary obstruction except by inference from and in association with subaortic obstruction. It is probably more common, but contrary to the disease of the left side the hypertrophy is usually secondary to valvular pulmonary stenosis[64] or large ventricular septal defects,[65] and is reversible after repair of the primary lesion.[66] The protective function in this latter anomaly, shielding the lungs against high flow or pressure, is reminiscent of the primitive function that Keith[70] postulated for the bulbus cordis (which evolves primarily into the right ventricular outflow tract) and which March[71] demonstrated in sharks, turtles, and reptiles. Rodbard and Shaffer[72] early recognized the dynamic character of the muscular stenosis of the right ventricular outflow tract from the asynchrony of peak pressures in the right ventricular cavity and infundibulum. The response to isoproterenol is similar to that in left ventricular obstruction.[73] Pronethalol has been used[74] to decrease the degree of pulmonary stenosis and thus improve arterial oxygen saturation in patients with tetralogy of Fallot, both at rest and after exercise. Vogel and Blount[75] used a pulmonary vasodilator (tolazoline) in patients with ventricular septal defect and pulmonary hypertension in order to reduce the afterload and "unmask" a gradient.

Therapy

After discouraging first attempts at surgical relief of obstructing septal hypertrophy, several operations have been advocated, some with apparent reasonable success. Morrow, Lambrew, and Braunwald[25] have reviewed the current status of surgical procedures in detail. Deep incision into the septal obstruction until a plane is reached at which further separation of muscle layers is spontaneous was suggested by Cleland[76] and used by Wigle and associates.[26] Kirklin and Ellis[76] and Julian and co-workers[77] resected the obstructing muscle through an anterior ventricular approach, whereas Swan[78] resected septal tissue with a cork borer inserted through the ventricular apex. Lillehei and Levy[79] and Dobell, Scott, and MacLean[100] advocated a transatrial approach with detachment of the anterior mitral leaflet for optimum visualization of the hypertrophic lesion and to clarify the relation of the mitral valve to the obstruction. Harken[81] advocated a right ventricular approach to the septum. It is clear that a definite technique is yet to be devised. Indeed, it is not certain that resection of tissue is the desired aim of surgery, since deep ventricular septal myotomy with or without the production of left bundle branch block has occasionally been effective.[26] Brock[82] sounded a note of caution for the validity of a surgical approach to a generalized myocardial disease. At present, surgical excision of the hypertrophic septal mass is recommended when there is direct evidence of significant obstruction in the resting state in a symptomatic patient, i.e., a gradient of 50 mm. Hg or more. In subjects with small resting gradients or large gradients produced by pharmacologic stimuli or in those with a family history of sudden death, surgery is not yet advocated. Medical therapy may be indicated in these subjects. Methoxamine relieves the obstruction but is not suitable for long-term use. In 3 patients[4] chronic therapy with β-adrenergic blockade aggravated

toms in 2 reserpine decreased symptoms in 2 patients.[19] Caution should be exercised in treating patients for congestive failure or preoperatively with digitalis or inotropic sympathomimetic amines such as norepinephrine or metaraminol. Furthermore, although the hemodynamic significance of the obstructive component seems to be clear, it should be remembered that patients with idiopathic hypertrophy even without obstruction may nevertheless suffer from angina or congestive failure and be subject to sudden death.

Conclusions

Several varieties of cardiomyopathy have been defined in recent years, among them a hypertrophic obstructive form. This form is frequently familial and presents with evidence of obstruction of the left ventricular outflow tract and generalized but frequently asymmetrical hypertrophy of the left ventricle. Unlike more discrete forms of obstruction of the outflow tract, it is a dynamic lesion susceptible to manipulation by pharmacologic or physiologic maneuvers, the clinical equivalent of which may be the cause of sudden death. The pathologic abnormalities are few and nonspecific but histochemistry may soon shed more light. Surgical therapy of the obstructive aspect of the cardiomyopathy is being developed.

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Antiarrhythmic drugs
Part II Clinical use of quinidine

*Alan F Lyon M D**
*Arthur C DeGraff M D***
New York N Y

Although it is not certain whether the therapeutic effect of quinidine is related primarily to its capacity to slow depolarization of muscle cells to prolong their refractoriness or to inhibit spontaneous diastolic depolarization it is clearly related to its effect on the muscle cell membrane. This effect is probably proportional to the concentration at the membrane rather than to the serum or over all intracellular concentration. It is not surprising then that there are discrepancies between serum level and therapeutic or toxic effects these latter sometimes occurring while the serum level is declining. The use of the serum level to quantitate the effect of quinidine is further complicated by the presence in the serum of dihydroquinidine which contaminates most quinidine preparations and of several hydroxylation products of the metabolic breakdown of administered quinidine. All these substances will be included in the ordinary photofluorometric assay of quinidine unless as is not ordinarily done the compounds of the quinidine group are first separated by chromatography.

Despite these disadvantages information gained from the clinical correlation of the serum level of quinidine with its therapeutic and toxic effect has supplied a rational foundation for dosage schedules of quinidine. A significant and often adequate electrical depression of the heart is seen with blood levels between 3 and 5 mg per liter. Levels between 5 and 8 mg per liter are therapeutic in the majority of instances. The average concentration at the time of conversion of atrial fibrillation has been shown to be 5 4 mg per liter. On the other hand quinidine toxicity is rare below 6 mg per liter and occurs in only 12 per cent of patients whose blood level falls between 6 and 8 mg per liter. Levels between 8 and 10 mg per liter are associated with toxicity 30 per cent of the time levels over 14 mg per liter 45 per cent and levels over 14 mg per liter 65 per cent. Thus although individual differences exist a discernible pattern of dose relationship is present.

The level of quinidine in the serum is not readily available to most physicians. However in most situations it has proved to be adequate to use the information gained from its study to use oral dosage schedules more reasonably. It has been shown that the peak level in the blood after a single oral dose occurs in 2 or 3 hours that by 4 hours the level is beginning to fall that it is one half of the maximum by 8 hours and that no detectable quinidine is noted in

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*Cardiac Therapy Research [illegible] Hospital [illegible] Bronx, N. Y. [illegible]

**Department of Therapeutics New York University School of Medicine 550 First Avenue New York N. Y. 10016

the blood in 24 hours The conclusion is that any multiple dose schedule will produce accumulation of quinidine in the serum and presumably at the cell membrane until a balance between absorption and dissipation is achieved When quinidine is given orally every 2 hours at the same dose a peak level in the blood is achieved as a rule after the fifth dose Continued administration of the same dose every 2 hours will produce little further increase in the level in the blood When the same dose is given orally every 4 hours maximum levels in the blood are achieved in 48 to 72 hours When the drug is given every 6 hours or even on a four times-a-day schedule there is some carry-over to the next day and the highest blood levels achieved may not be recorded until the fifth day

Unfortunately in addition to the individual variation in the blood level at which the therapeutic effect takes place there is wide variation between subjects in the blood levels produced on a given oral dose schedule At a total dose of 3 0 Gm a day there may be a fivefold variation in the level of quinidine in the blood Since quinidine sulfate is almost completely absorbed these differences must result from differences in rate of absorption rate of renal excretion and especially rate of metabolic degradation in the liver (Between 20 and 30 per cent of an administered dose of quinidine is excreted unchanged in the urine and the rest is degraded primarily in the liver and generally by the production of hydroxylation products)

Although the presence of liver or kidney disease has not been shown to affect the metabolism of quinidine prolonged elevation of blood level and effect have often been found in the presence of congestive heart failure

Dosage schedules Because of this wide individual variation a certain amount of trial and error is necessary before the proper dose for each patient is established For the prevention of the recurrence of a tachycardia or fibrillation 0 4 Gm of quinidine sulfate may be tried initially every 6 hours or on a four times a-day basis This will provide effective suppressive therapy in most patients If toxic manifestations should occur the dose can be adjusted It seems unwise to begin with a smaller frequently ineffective dose because tachycardia or fibrillation would then be more likely to recur On the other hand when the goal of therapy is to suppress recurrent but isolated ectopic beats therapy could reasonably be begun at 0 2 Gm four times a day and then increased at 5-day intervals until the minimal dose which will suppress the ectopic beats is achieved

Occasionally larger doses will be necessary to suppress an arrhythmia either because of inadequate levels in the blood or because adequate levels in the blood are ineffective In this situation determination of the serum level would be very valuable If it is low a larger dose of the drug may be given with safety if the level is 7 or 8 mg per liter the dosage should not be increased except for the control of a potentially life threatening arrhythmia

The standard drug for maintenance therapy is quinidine sulfate which represents 83 per cent quinidine base It is available as a 200-mg uncoated tablet

Long acting preparations usually of the gluconate salt (62 per cent quinidine base) are available Although these preparations are said to be more convenient ordinary quinidine sulfate given in adequate dosage on a four times a-day basis maintains adequate levels in the blood through the night so that early morning escape should not be a problem

A reasonable convenient and widely used schedule involves the administration of five equal doses of quinidine at 2 hour intervals during the day With an early morning start the maximum levels in the blood are achieved in the evening and no middle-of the night monitoring is necessary If this is unsuccessful the same schedule should be repeated the next day because there will be some quinidine persisting from the previous day and the serum levels will be higher The initial dose should be 0 2 Gm five times a day with increments every 2 days of 0 1 Gm at each dose until the arrhythmia is terminated toxicity supervenes or a total dose of 3 0 Gm in 24 hours is achieved When larger doses are used electrocardiographic monitoring for signs of toxicity such as prolongation of the QRS interval or the ap-

pearance of ventricular premature contractions is necessary. Also the blood pressure should be taken frequently because of the hypotensive action of quinidine.

Similar results can be achieved by the regular administration of quinidine every 4 hours, but this inconveniences the patient and doctor in that nocturnal administration and monitoring are necessary, and another disadvantage is that the dose cannot be increased with relative safety until maximum accumulation has occurred (72 hours on this schedule). Other schedules of administration which may require a faster rate of dosage increment at either 2 hour or 4 hour intervals would seem to be significantly more hazardous.

When quinidine or drug therapy was the only way to terminate arrhythmias, it was our custom occasionally to use doses above 3.0 Gm. in 24 hours if serious toxicity did not prevent it. Above this dose, however, the likelihood of terminating the arrhythmia decreases. For instance, with 3.0 Gm. in 24 hours the overall success in terminating atrial fibrillation is 70 to 80 per cent; above 3.0 Gm. the rate of success falls to 30 per cent. Furthermore, above 3.0 Gm. the likelihood of severe toxicity greatly increases. At this dose, quinidine becomes more hazardous and less successful than synchronized countershock and should not be used.

Minor cardiovascular toxicity, such as the appearance of a few ventricular premature contractions or less than 25 per cent widening of the QRS complex, may not preclude further quinidine therapy. However, any cardiac or central nervous system manifestation of toxicity prior to termination of the arrhythmia so increases the hazard of the procedure compared with countershock that the attempt to convert with quinidine should be discontinued and synchronized countershock used. Minor gastrointestinal toxicity that can be symptomatically controlled does not preclude the use of quinidine.

When quinidine therapy is ineffective in the conversion or suppression of an arrhythmia, it may be possible to add procaine amide with added and possibly synergistic therapeutic effect and less increment of toxicity.

Reports in the literature suggest that the parenteral use of quinidine involves significant hazard, with a 10 per cent mortality rate in one series. It is more hazardous than either parenteral procaine amide or synchronized countershock. Quinidine sulfate, lactate, and gluconate are available for parenteral use, and all achieve a peak level in the blood in 5 minutes or less and a maximum clinical effect in 15 minutes.

Indications for use of quinidine. With increasing clinical success in the termination of atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation, there are increasing indications for chronic suppressive therapy. In the latter role, quinidine remains the drug of choice, being probably superior in efficacy and certainly *lower* in cost than the only *other* extensively used drug, procaine amide. Only when allergy or idiosyncrasy precludes the use of quinidine should procaine amide be used. The role of quinidine in the termination of tachycardias is much less certain. It has been largely supplanted by procaine amide and synchronized countershock in the treatment of ventricular tachycardia. Atrial flutter, when digitalis alone has failed, responds to quinidine rather inconsistently. This rhythm is very susceptible to synchronized countershock; we believe that this is now the method of choice. The role of quinidine in the treatment of atrial fibrillation is uncertain. Although other studies indicate a mortality of between 1 and 2.5 per cent, the doses were considerably higher than those used today. Conversion to regular sinus rhythm with quinidine as described above is relatively safe and synchronized countershock has not as yet been proved to be safer. For the present, then, we believe that the oral use of quinidine is still the first treatment for atrial fibrillation when conversion is indicated.

Another unresolved problem is the place of prophylactic quinidine in the presence of acute myocardial infarction. One would not wish to use this drug, which depresses not only the electrical activity of the heart but also its contractility and peripheral vasomotor tone, unless there were good evidence that it reduces morbidity and mortality. There appears to be no well-controlled study that shows such an effect

so that a clinical basis for such use of quinidine has not been established

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Indicator dispersion in the circulation*

Stewart [illegible] 1897 was one of the first to observe that a bolus became increasingly dispersed as it traveled through the vascular system. He noted that for a bolus of injected saline the time between first appearance at the femoral artery and maximal concentration was longer when injection was made into the right ventricle than when made into the left ventricle. This [illegible] to be expected whether flow is laminar or turbulent.

In general, dispersion in the circulation is due to four distinct types of processes: (1) velocity profile produced by differences in the velocities of particles at different distances from the wall of a vessel; ([illegible]) mixing pool effect such as occur in eddies or cardiac chambers which exchange [illegible] proportion of their volume with the blood flowing through or past them; (3) random movement of particles backward, forward, and [illegible] the stream in turbulent flow; and (4) differences in length of parallel pathways through the capillary network of an organ or through different regions of the body.

Velocity profile. The simplest example of nonuniformity of velocity of flowing liquid was demonstrated by [illegible] 1840. During steady flow of homogeneous fluid through smooth straight cylindrical tubes, the velocity is greatest at the axis of the tube and decreases parabolically to zero at the wall. However, this parabolic laminar flow cannot occur [illegible] the circulation[4] because erythrocytes prohibit the existence of very thin laminae; flow is not steady long enough for disturbances to die away; and vessels are tapered and branching. In parabolic flow the ratio of maximal to average velocity is 2.0. Indicator-dilution studies in circulatory models, in dogs, [illegible] in human subjects [illegible] and in catheters filled with blood resulted in observed ratios of 1.6 to 1.7. Such values indicate that the velocity profile is more blunt than a parabola, which undoubtedly [illegible] due partly to the fact that erythrocytes tend to travel in the center of the stream,[4] and trap plasma between them.

Mixing pools. The concept of a mixing pool effect or exponential washout was introduced by Hamilton and co-workers who observed that the decay slopes of concentration-time curves recorded after the injection of a slug of dye could be closely described by a single exponential—that is, the downslope formed a straight line when plotted on semilog paper. A perfect mixing chamber is one in which all of its volume is continuously and instantaneously mixed and the proportion of fluid leaving is F/V, the flow divided by the volume, or the time constant is V/F seconds. Logically, Holt[illegible] has applied this concept to the washout of indicator injected into a ventricle; thus when the cardiac output is known, the end-diastolic and end-systolic volumes of the ventricle can be calculated. The ratio of stroke volume to end-diastolic volume is less when determined by this method than when estimated by angiocardiography, and therefore the completeness of the mixing has been questioned. Application of mixing pool washout models to the central circulation[illegible] is an exercise in curve fitting—matching a sum of exponentials to recorded dye-dilution curves. Volumes calculated from V/F ([illegible] slope volumes, for example) have no apparent physiologic definition.[illegible]

Random movement of particles. After a single injection at an upstream site, a concentration-time curve recorded from the circulation is remarkably like a Gaussian distribution curve skewed to the right until recirculated indicator mixes with that passing by the sampling point for the first time. Random (Gaussian) dispersion of indicator occurs at the extremes of flow rates. Dispersion by diffusion in fluid flowing very slowly in capillary tubes is Gaussian,[illegible] and results in less spread of the bolus than is found with parabolic flow alone. Random dispersion was also observed in highly turbulent flow in oil pipe lines[illegible] and in water in smooth or rough pipes.[illegible] The great longitudinal dispersion associated with parabolic flow is due to relatively low velocities in the laminae near the wall of the tube. With very slow flow there is time for indicator to diffuse toward more central faster flowing laminae. In the violence of turbulent flow the disparity between mean axial velocity and mean velocity near the wall is lessened. Taylor[illegible] and Hull and Kent[illegible] found that the dispersion in straight tubes of uniform diameter (as measured by standard deviation of the concentration-time curve or spread between [illegible] of chosen concentration levels on the curve) was in proportion to the square root of the distance traveled.

Arriving at the same conclusion completely independently by primarily theoretical reasoning, Sheppard[illegible] proposed the use of the random walk

*Th[illegible] [illegible] supported in part by Research [illegible] HE [illegible] from the National Institutes of Health, United States Public Health Service. Dr. [illegible] is the recipient of a Research Career Development Award from the National Institutes of Health and Dr. [illegible] Research Career Award from the National Heart Institute.

equation as a mathematical model for dye-dilution curves. The random walk equation is certainly an esthetically pleasing model for circulatory dispersion; it describes the concentration-time curve obtained at a sampling point when a bolus randomly dispersed with respect to distance passes by. The model describes dispersion within columns of glass bead but does not describe dye curves from the circulation very closely unless the time origin and rate of spreading are changed to make the curve more skewed. The skewness of recorded dye curves may be explained by either the existence of lower velocities near the wall or by eddy formations acting as mixing pool.

The lagged normal density curve, a model which combines random dispersion with exponential washout, has recently been extensively investigated by Bassingthwaighte, Warner and Wood. The equation has been shown to closely approximate arterial dye curves whether the injection was made into a vena cava or into the aorta, and whether cardiac output or peripheral arterial flow was high or low.

Dispersion may be characterized numerically by calculating the variance (the second moment) of the dye curves or the breadth between chosen points on the curve. The data of Korner[a] and of Bassingthwaighte[1] indicate that the standard deviation (the square root of the variance) or the breadths (from appearance time to mean transit time) of dye curves obtained over a wide range of flow rates were linearly related to mean transit time from injection site to sampling site. This indicates that flow has little or no influence on the rate of longitudinal or spatial dispersion. In normal men dispersion was greatest within the heart and lungs, less in the aorta, and least in the peripheral arterial segment between the femoral and dorsalis pedis arteries. Edwards and Korner[a] noted that in dogs dispersion was less in the inferior vena cava than in the thoracic circulation.

Recorded dye curves are the result of dispersion by at least three mechanisms: (1) dispersion produced by the force of injection and by the duration of injection, (2) circulatory dispersion, and (3) dispersion by the sampling system. If the injection of dye is made somewhere upstream and dye curves are recorded from two sites simultaneously by means of identical sampling systems with identical sampling flow rates, then one can compute the transfer function between the two sampling sites. The transfer function is a description of the dispersion and delay occurring in that segment and is completely independent of dispersion at the site of injection and by the sampling system. The lagged normal density curve serves well as the transfer function for the segment of the arterial system between the femoral and dorsalis pedis arteries of normal men, and the dispersion of the transfer function was, as for the recorded curves, linearly proportional to the mean transit time between the sampling sites, indicating the lack of influence of flow rate (over an eightfold range above normal flow) on the rate of spatial dispersion.

Dispersion due to differences in path length. The greater dispersion in the thoracic circulation than in the systemic arterial system is due in part to differences in the lengths of and the velocities in different pathways through the capillary bed of the lung, and in part to the mixing pool effect of the cardiac chambers. Parrish and co-workers[a] recorded dye curves from the pulmonary arteries and pulmonary veins of dogs and computed the transfer function between these sites. In general the transfer functions appeared to be random distributions with some skewing to the right—they were very similar to lagged normal density curves. The latter model has been found to be suitable for describing transfer functions through the lungs, heart and kidney.[a]

Dispersion is much less through a compact organ than it is over the great differences in path lengths between various organs and in particular in the limbs. Moreover the limbs not only have the longest paths but may also have the slowest velocities, for example in skin exposed to a cool environment. Nicholes and co-workers[a] have suggested a model for the whole circulation describing it by transfer functions for specific organs or groups of organs in series and in parallel. Although the details are far from complete, primarily because of the difficulty in distinguishing indicator arriving for the first time through slow paths from that recirculating through faster routes, they have been able to use it to show that exercise increases the proportion of the cardiac output flowing through paths with short transit times. Such analyses also provide a method for determining the flows through these pathways. Flow through specific organs may be estimated if the traversal times of indicator passing through the organ to the central venous circulation can be distinguished from traversal times through other organs.[a]

GENERAL COMMENT. The fact that the rate of spatial dispersion in a series in the leg is unaffected by flow rate strongly suggests that there was no change in flow characteristics in these arteries even when a sixfold to eightfold change in flow rate occurred. Since flow was almost certainly turbulent at the highest flow rates, it is very likely that it also was turbulent at normal flow rates. It must be emphasized that even in turbulence the longitudinal velocity is not constant at all points in a cross section, but velocities at the wall may be slower than central velocities, nor is lateral mixing necessarily complete across the cross section (it usually is not). Thus the existence of stream lines can be expected in arteries in spite of turbulence, and the observation of streaming in the aorta in no way justifies the assumption that the flow is laminar. By definition, in laminar flow the stream lines remain intact, but streaming in highly turbulent flow is very common—for example the water of two confluent rivers may remain distinguishable for miles in spite of Reynolds numbers of several hundred thousand and obvious localized turbulence.

In spite of the general belief that more dispersion should be produced by turbulence than by laminar flow, mathematical theory and actual observation show that the truth is just the opposite. The presence of turbulence tends to maintain the bolus of indicator in a more intact form, for there is less thickness of slow or stationary fluid at the wall. If this were not so, or if parabolic laminar fl

prescnt t would almost certainly be impossible t measure either cardiac output or mean circulation times by indicator dilution techniques in the ir ulation for the t il of the curves would be so pr longed th it t would be impos ible to eparate the re irculating indicator from th t passing for the fir t t me B m lar reason ng t highly un lik ly th t p r b l l minar flow exists even in the ocu s tem t an gre t extent although t ming much m r l kely to occur i veins tha arter es

J mes B Bassingthwa ghte M D Ph D
Section of Physiology
M o Clinic Rochester Minn
Homer R W rner M D Ph D
D p rtment of Biophysics and Bioengineering
University of Utah
Salt Lake City Utah

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Effect of altitude (hypoxia) on coronary artery size in the white rat*

In 1944 Amadeo[1] alluded to a protective effect of anemia against coronary artery disease in Puerto Rican with hookworm disease Zoll Wessler and Schlesinger[2] demonstrated increased coronary arterial anastomoses in the hearts of patients who died with anemia Their studies also demonstrated a less than expected incidence of myocardial infarcts in anemic patient whose coronary arteries were occluded Results of experimental production of anemia in pigs by Zoll and Norman were congruent with the human autopsy studies Eckstein showed an increased retrograde coronary blood flow in severely anemic dogs after occlusion of a coronary artery Tepperman and Pearlman demonstrated an increased size of the coronary arteries in anemic ducklings The opposite of anemia an elevated blood hematocrit was found by Burch and DePasquale[6] in patients with acute myocardial infarction

It was chosen to determine whether hypoxia without anemia would influence the size of the coronary arteries of young white rats Simulated altitude in a low pressure chamber was elected as a straightforward method to produce controlled hypoxia Young male white rats (150 grams) and their litter mates were selected for study For 2 hours a day for 15 days 20 rats were placed in a vacuum jar at a simulated altitude of 2 000 feet producing a pO of 67 mm Hg in the chamber Three rats died during the experiment

At sacrifice the animals were weighed and the coronary arteries were injected Following Tepperman and Pearlman method amyl acetate was injected into the aorta to fill the coronary arteries The heart after being weighed was digested The coronary casts were carefully trimmed and weighed on an electromagnetic balance to the nearest 0 1 mg Satisfactory injections were achieved in 16 experimental animals and 20 controls

The mean weight of the coronary artery casts from animals submitted to hypoxia was 5 6 mg that of controls was 3 1 mg (t = 4 87 p < 0 01)

In [illegible] with the [illegible] M D and M Bautner were [illegible] (1963) between Research Fellowship [illegible] provided by the Health and [illegible] Association of Genesee County

The ratio of coronary artery cast weight to heart weight was significantly greater in the exposed rats (6 35 versus 3 38 mg per gram t = 4 01 p < 0 01) A slight loss in body weight occurred in the experimental animals (mean of 247 grams 296 grams) Ratios of heart weight to body weight were slightly increased in the experimental group (0 388 versus 0 313 per cent) Hematocrits in those made hypoxic averaging 57 5 as against 46 3 for control

It is concluded that hypoxia without anemia produces significant growth of coronary arteries in young rats Whether a similar increase in the size of the coronary arteries can be produced by hypoxia without accompanying cardiac hypertrophy and accompanying elevation of hematocrit remains to be determined

Andrew Kerr J M D
Robert B Diasio
William J Bauerer
Cardiopulmonary Laboratory
Veterans Administration Hospital
Batavia N Y 14021

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Experimental necrosis of the anterior pituitary

N s f the anterior pitu tary occurs in human l s rious c nd tion (diabetes mellitus, r sed nt ac anial pres ure etc) but it is most frequently observed obstetric patients in whom d l ery ompl ted by severe circulatory collapse u uall due to los of blood If the pituitary necr si ery exten iv nd the patient urvives hronic h popituitari m—Sheehan syndrome—develops

The m rph logic changes taking place in the pitu taries the human ses ha been studied recentl n deta l by Sheehan and Stanfield The lesion h all the haracteristics of an infarct and mu t therefore be nsidered to be a result f v scular oc lusion The nature of the local circulatory di turbance t qu te clear but vascular spa m ha been postulated to be the cause

Ma workers ha e tried to reproduce pituitary necrosis animal by arious method such as gi ing asocon trictor substances to normal animal or t nimal pretreated w th hormones or by bleed ng severely t the time of deliv ry However these effort ha e been un ucces ful

A reported in a recent paper nterior pituitary necr si has bee ucces fully induced in rat by dmin tering the qu ternary ammonium salt hexadimethrine bromide With a single intravenous or intraperitoneal njection of 3 to 10 mg about one half of the animal develop necrosi of the anter r lobe There re no lesions n the intermediate and poster r lobes The morphologic changes in the anter r pituit ry are typical infarcts and are remarkabl y simila to those which occur in postpartum pituitary necrosis in human patients

It is well known that destruction of the pituitary talk either by electrocautery or b operation causes varying sizes of necrosis of the anterior pituitary n human being and also in some species of animals[3] These urgical intervention h wever nterrupt the nerve fibers in the talk and lead to severe atrophy of the poster r l be which complicates the tudy of anterior hypop tu tari m Moreover there is a tructural d sruption f the port l vessels to the anterior lobe and lthough these vessel are abl to regenerate subsequentl the tran fer of release factors from the hypothalamu to the pitu tary most ertainly be impaired or ar rested for a long perio l of time Unfortunat ly hexadimethrine brom de causes ha ges in rious other organs and some of these les on can be fatal in a few da so that the acute n l chronic functional d turbances of the anterior pituitary cannot be stud ed sati factorily at present Nevertheless the use of thi experimental model ha permitted the study of some general factors concerned in the pathogene is of necrosis of the anterior pituitary

Since no thrombi could be found in the sinu oids or portal vessels of the pituitary during the pre necrotic phase primary thrombosis cannot be accepted as having any role in causing the necrosis Thrombi develop in some of the necrotic sinusoids in the marginal zones of the infarcts at about 12 to 24 hours and can still be seen there during the next few days but this thrombosis is adequatel explained as a secondary change that occurs in the previously damaged va culature The exact site and nature of the local vascular disturbance is not yet clear these problems need further study

Hexadimethrine was given to normal pregnant rats which were at term but the incidence and extent of the pitu tary necrosis in the pregnant animals was certainly not greater than in nonpregnant control animals This finding is in striking contrast to the ncidence of pituitary necrosi in women at deli ery Pretreatment with large doses of estrogen increased the severity of the pituitary lesion the necrosis wa usually very extensive and occurred i almost every an mal[4] Numerous other hormones and pharmacologic substances have been given i a sociation w th the hexadimethrine but did not produce significant d fferences from the lesions induced by hexadimethrine alone On the other hand if an adequate amount of heparin is given in a oc tion with the hexadimethrine the substances combine chemically to produce an inact ve compound A a result there is no pituitary necrosis and the other lesions produced by hexadimethrine are also prevented Although the complete neutralizing effect of heparin i of interest it throw little l ght on the pathogenesis of the hexadimethrine induced lesions

Hexadimethrine bromide causes d ruption of ma t cells and thus the liberation of the constituents of mast cells into the circul ition It seemed reas nabl therefore to study whether the con tit uent of mast cell play any role in ca ing the necros of the anterior pitu tary When the mast cells of rats were depleted b pretre tment w th C mpound 48/80 no pitu tary necrosis devel ped after the adm trat n f hexadimethrine Serot n depl ters or serot nin antagonist were w th o t any marked effect On the other han l pretreatment w th a h tamine depleter (polymyxin B) or the admin tration of t h tamines definitely reduced the severity of the pituit ry necr s caused by hexadimethrine Therefore t seems that the presence of adequate tores of h tamine is a pre

requisite for the production of the pituitary lesion These findings suggested that histamine may have some part in the pathogenesis of hexadimethrine induced necrosis of the anterior pituitary However the lesion could not be reproduced by the administration of exogenous histamine alone or of histamine releasers without hexadimethrine Thus at present it has not been proved that the effect of hexadimethrine on the anterior pituitary is mediated through the release of endogenous histamine

Further experiments are needed to elucidate the detailed pathogenesis of the pituitary necrosis caused by hexadimethrine Nevertheless one fact is clear hexadimethrine induced necrosis seems to be a suitable experimental model for the study of various unsolved problems concerning the pathogenesis of pituitary necrosis and the subject of anterior hypopituitarism

K Kovacs MD
R Carroll MD MRCPI MCPath
E Tapp MD
Department of Pathology
University of Liverpool
Liverpool England

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A plea for precision in cardiovascular description*

The increasing number and variety of methods for assessing blood flow quantitatively threatens to increase the possibility of confusion and misinterpretation in the construction of a unified description of the circulation To slow the onset of chaos we plead for a more self-conscious attention to the difference between (a) what is actually measured (the experiment) and (b) the mental picture of what is presumed to be happening (the theory)

The measurements obtained in any experiment represent numerical values of physical quantities The properties of a physical quantity are (1) a description or definition (2) dimensions and (3) units For example blood flow is the volume of blood passing a cross section in unit time and has the dimensions L³T⁻¹ and a unit such as ml/min which conforms to the dimensions and definition and is of a convenient and rational size Failure to state precisely all of these characteristics of the measurements often leads to confusion

One area in which misunderstandings have already arisen is that of relating measurements of local clearance of sodium xenon colloids or heat to total blood flow measured by venous occlusion plethysmography electromagnetic flow meter direct Fick method or dye dilution Consider a local clearance experiment in which the rate of disappearance of radioactive sodium ions from a small region of leg muscle is measured According to one theory this experiment implies that the ratio of blood flow in nutritive vessel (ml/min) to *extracellular volume* (100 ml) in a small region of leg muscle tissue for example 5 ml/min/100 ml (using an appropriate tissue/blood distribution coefficient for sodium etc) According to another (hypothetical) theory the same experiment might imply that the ratio of blood flow in certain types of venules (ml/min) to *total tissue volume* (100 ml) in the same region of leg muscle is 3 ml/min/100 ml The preceding numerical values cannot be

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Book reviews

HERZAUSKULTATION. By Rudolf Zuckermann, Dr Med Habil, Professor mit Lehrstuhl für Kardiologie, Martin Luther Universität Halle. Leipzig, 1963, Georg Thieme. 287 pages. Price DM27.40

After a comprehensive discussion about the theories of heart sounds and murmurs, the author elaborates on the auscultatory phenomena of acquired and congenital valvular diseases. This is followed by a description of the findings in degenerative and inflammatory myocardial diseases and in various atrioventricular and intraventricular conduction disturbances. In this book, Zuckermann intentionally disregards the other routine cardiological investigatory methods. The wealth of data presented will be appreciated by the practicing cardiologist, although it may provide some difficulties for the medical student. Reference in the text to the excellent phonocardiographic photographs in the appendix would be desirable. Worth mentioning is the systematic arrangement of the bibliography, which readily facilitates location of the original literature.

DIE PROGNOSE DER ESSENTIELLEN HYPERTONIE. By Prof Dr Klaus Kuhns and Dr Med Otto Brahms. Darmstadt, 1964, Dr Dietrich Steinkopff Verlag. 119 pages

This monograph describes the results of a detailed study and follow up of 4,379 patients seen in a special clinic for hypertensive subjects which was organized at the University of Gottingen in 1950. As pointed out in the introductory remarks of Professor R. Schoen, the primary purpose of this clinic was to make long term observations on the prognosis of essential hypertension, especially as it might be affected by modern treatment.

The authors' findings in regard to prognosis are presented in ten sections in relation to (1) age and sex, (2) body weight, (3) level of blood pressure, (4) occupation, (5) heredity, (6) cardiac findings, (7) renal findings, (8) eye ground changes, (9) subjective symptoms, and (10) pharmacologic therapy.

Most of the correlations discussed confirm the findings of previous similar studies. Some findings which seem to be worth calling to the attention of the reader are the following:

1. Dividing the patients into overweight, normal weight, and underweight categories, the authors found the worst prognosis in the underweight group, and this was more clearly seen in male patients.

2. In men and women over 60 years of age, instead of a gradual increase in the death rate with rising diastolic pressure, there was a maximum rate for diastolic pressures in the 90-109 mm Hg range.

3. If the severe changes in the fundus of the eye associated with renal and malignant hypertension were excluded from consideration and attention was focused on uncomplicated essential hypertension, the authors found that eye ground changes were of limited value in assessing the prognosis.

4. The treated group showed a significantly better survival rate than did the untreated group. Noteworthy is the fact that this increased survival rate was quite apparent, especially with the use of rauwolfia alkaloids, even though the falls in blood pressure which were achieved were often negligible. (Newer drugs such as guanethidine and methyldopa were not in use long enough to be evaluated.)

The book is recommended to those who plan similar studies in large groups of hypertensive patients but not to the student or practitioner in general.

IL CAMPO ELETTRICO CARDIACO. By Massimo Obbiassi. Milan, 1964, Recordati. 139 pages

The standardization of the method of derivation and the definition of the relationship between the spatial vectorcardiogram and the standard electrocardiogram is still today one of the most interesting problems open to discussion and research.

In fact, the real complexity of the biologic phenomenon of the electrogenesis of the heart does not allow theoretically a vectorial synthesis of the heart electrical field. The necessity exists of somehow simplifying the phenomenon by transforming the complex cardiac generator to a simpler one and the human body to a more homogeneous conductor. This procedure has necessarily produced some differing theoretical and practical opinions, so that consequently the results are not always in agreement.

The mass of studies devoted to this subject are immense, and Obbiassi in his monograph makes a detailed analysis of the subject, setting forth the whole problem.

After a clear statement of the electrophysiologic bases, the author analyzes the hypothesis of the single dipole, its localization, the determination of the axes of derivation, and the theory of the derivation field, examining too the most important systems of derivation used up to the present time.

The conclusions which the author reaches are essentially open to question, and it could hardly have been otherwise in light of the fact that this work is chiefly a review of the literature.

In my opinion this study is a very useful premise for an ultimate examination of the analogies and points of similarity between apparently contradictory theoretical concepts, and for undertaking a systematic check and comparison of the methods, all of which seem to be the only suitable procedures in the search for definitive explanations.

Announcements

MEDICAL RESEARCH GRANTS AND FELLOWSHIPS The Life Insurance Medical Research Fund is now receiving applications for award to be available July 1 1966 as follows *Until Sept 15 1965* for grants to institutions in aid of research on cardiovascular problem Support is available for physiological biochemical and other basic research with some preference given to the cardiovascular area Further information and application forms may be obtained from the Scientific Director Life Insurance Medical Research Fund 1030 East Lancaster Ave Rosemont Pa 19010

The Fund also offers a maximum of 6 years of full fellowship aid to medical students willing to prepare for careers in teaching and research by securing both the M D and the Ph D or its equivalent Each school of medicine is invited to make one nomination for a fellowship to begin July 1 1966 Fellowships have been activated at various stages of M D Ph D training Deadline for receipt of applications from the deans offices is *Oct 1 1965* Further information can be obtained from deans in schools of medicine

JANE NUGENT COCHEMS COMPETITION The University of Colorado School of Medicine announces the fourth Cochems Competition funds for which were provided in the will of the late Mrs Jane Nugent Cochems A prize of $2 500 will be awarded to the author of the best paper in the field of Thrombophlebitis and Basic Vascular Problems Basic vascular problems under consideration in this instance should be concerned with the underlying mechanisms or processes of vascular disease particularly those associated with thrombosis but not necessarily restricted to it

The competition is open to all persons holding the M D degree and entries must be received in triplicate including all charts *illustrations and* photographs on or before *Nov 15 1965* For income tax reasons eligibility is limited to those physicians who are subject to United States income tax regulations

The Colorado National Bank of Denver Trustees under the will of Jane Nugent Cochems has requested the Dean of the University of Colorado School of Medicine to conduct the competition The judges appointed by the Dean are Dr Sol Sherry Professor of Medicine Washington University School of Medicine St Louis Mo and Dr Michael E DeBakey Professor and Head of the Department of Surgery Baylor University College of Medicine Decisions of the judges are final and they may elect at their discretion not to award the prize

Papers submitted in the competition may not be published until after the winner has been announced early in 1966 At that time the winning paper and all others may be published at the discretion of individual authors It should be noted however that sponsors and judges of the competition will not assume any responsibility for submitting manuscripts for publication or for any costs incident thereto The winning paper if published must carry the designation Awarded the Jane Nugent Cochems Prize

No entry blank or application form is required There are no restrictive rules regarding length or format of the manuscript joint authorship or inclusion of such material as pictures charts figures etc It is not required that the paper include results of original experimental work or that it be based on personal clinical experience All manuscripts must be typed with double spacing and each copy together with accompanying illustrations etc must be submitted in a folder or cover On request the original copy of the manuscript will be returned if accompanied by a stamped addressed envelope Papers will be judged on originality content clarity and critical value

Inquiries in regard to the competition and all manuscripts should be submitted to Dr John J *Conger Vice President for* Medical Affairs and Dean School of Medicine University of Colorado Medical Center 4200 East Ninth Ave Denver Colo 80220

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